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DISEASES OF CHILDREN

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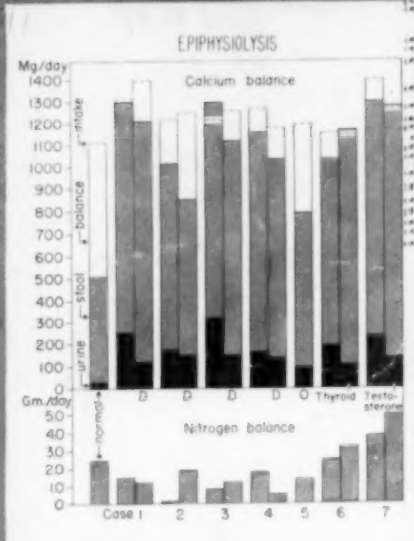

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A.M.A. Journal OF
DISEASES of CHILDREN

Total Body Water and Exchangeable Sodium in Normal Full-Term Newborn Infants

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During the past several years many clinical investigators focused their attentions on the measurement of bodily functions and compartments. Several methods for the measurement of the body's fluid compartments and electrolyte content have been developed and evaluated. These have been greatly facilitated by the application of isotopic tracer techniques. Values for the volumes of body compartments and their electrolyte contents have been established and the influence of various diseases on these moieties have been documented. Data on the total body water and electrolyte content of the newborn infant, however, have been somewhat limited.

Submitted for publication May 2, 1956; accepted July 10.

From the Department of Pediatrics and the Department of Medicine of the Stritch School of Medicine of Loyola University and Mercy Hospital.

This study was supported by research grants from the Prescription Products Division of the Borden Company and the United States Public Health Service Institute for Arthritis and Metabolic Disease A-430 (C).

This study was undertaken to measure the total body water and exchangeable sodium in newborn infants. The current report presents the data obtained by measuring the total body water and exchangeable sodium simultaneously in a series of normal newborn infants.

Subjects and Methods

Studies were made on 17 newborn infants ranging in age from 6 hours to 42 hours in the Newborn Nurseries of Mercy Hospital and Lewis Memorial Maternity Hospital. These infants and their mothers were in good health, without signs or symptoms of disease processes or anomalies. All studies were performed in a fasting state, i. e., before any feedings or oral fluids had been given. No oral feeding or fluid was given until eight hours after the time of injection of the test substances. No formula, only tea or water, was given until the last blood specimen was withdrawn.

A scalp vein infusion of 5% dextrose in water was started, then separately 7μc each of 4-iodantipyrine labeled with I^{131} and Na^{22} were injected. The method of infusion has been previously described in a recent article by Talso and coworkers.[1]

Blood samples were withdrawn at 4½, 6, 7, and 24 hours after injection. All specimens were collected in heparinized tubes and all analyses were done on the plasma obtained. A 24-hour urine sample was collected in each case; however, because of the difficulties in collection only boys were utilized in this study.

Radioactivity assays were made on 1-ml. aliquots of plasma using a well-type scintillation counter

with a single channel pulse-height analyzer. The method for the simultaneous determination of Na^{22} and I^{131} has been described elsewhere.[6] The concentration of 4-iodoantipyrine as expressed in counts per minute of I^{131} per milliliter of plasma (cpm/ml. plasma) were plotted against time on semilogarithmic paper. By extrapolation, the concentration at zero time was determined. This extrapolated zero time was then divided by 0.93 to correct for serum water content. By dividing the quantity of 4-iodoantipyrine injected as expressed in terms of I^{131} by this corrected zero time value, the volume of total body water was obtained.

Exchangeable sodium was calculated at the end of 24 hours, by measuring the radioactivity referable to Na^{22} in the 24-hour urine sample and subtracting this quantity from the quantity of Na^{22} injected. By dividing the amount of Na^{22} in counts per minute remaining at the end of 24 hours by the specific serum activity * the value of exchangeable sodium was obtained.

The sodium space was calculated by dividing the quantity of radioactive sodium remaining in the body at the end of 24 hours by the concentration of radioactive sodium found in the serum at this time.

Results

The results are shown in Table 1.

Serum Sodium. — As indicated in the Table, irrespective of age in hours (up to

* Serum Specific Activity $= \frac{Na^{22}\ cpm/ml.\ plasma}{Na^{23}\ mEq/ml.\ plasma}$

TABLE 1.—*Results of Body Water and Exchangeable Sodium Studies in Seventeen Full-Term Newborn Infants*

			Total Body Water			Na$_e$			
Case	Age, Hr.	Wt., Kg.	Kg.	% B.W.	Serum Na, MEq/L.	MEq	MEq/Kg. TBW	MEq/Kg. B.W.	Na Space, Ml/Kg. B.W.
1	6	3.10	1.92	62.0	152	270	140	87	572
2	36	3.05	2.06	67.5	157	230	116	79	500
3	18	3.77	2.32	61.5	163	323	139	86	525
4	25	3.38	2.00	59.2	145	286	143	85	584
5	42	3.27	2.37	72.5	152	315	133	96	633
6	32	3.15	1.91	60.6	153	256	134	81	530
7	24	3.98	2.76	69.4	152	356	129	89	588
8	21	3.38	2.25	66.6	158	304	134	90	569
9	22	3.04	1.92	63.2	149	230	120	76	508
10	24	2.64	1.79	67.8	147	227	127	86	584
11	34	3.04	2.00	65.8	146	253	127	83	570
12	24	3.24	2.35	72.5	150	273	116	84	559
13	26	3.50	2.58	71.9	149	296	115	83	554
14	30	3.37	2.41	71.5	151	295	122	88	580
15	26	3.35	2.25	61.2	159	333	148	99	623
16	21	3.39	2.62	72.9	147	285	109	79	541
17	24	2.98	1.77	59.4	160	270	153	91	566
Mean	26	3.29	2.19	66.2	152	283	130	86	564
S.D.	±7.9	±0.33	±0.3	±4.99	±5.31	±36.4	±12.4	±6.0	±35.9

42) after birth, the serum sodium is higher than previously reported values.† An unpublished study, completed on a group of 30 prematures by one of us (J. R. C.), revealed serum sodium levels even higher than those found in the present series of full-term infants.

Exchangeable Sodium (NaE). — Values listed for exchangeable sodium are rather difficult to evaluate or compare because of a paucity of such determinations in the literature. Camerer, and co-workers,[7] using a method of carcass analysis and desiccation on six newborn infants, found the exchangeable sodium to be 73.7 mEq/kg. Widdowson,[9] using a similar method in six newborn infants, found it to be 82.5 mEq/kg. The exchangeable sodium is expressed in Table 1 in millequivalents, millequivalents per kilogram, and millequivalents per kilogram of body water. This latter ratio is probably a more accurate means of expressing exchangeable sodium, in view of the fact that exchangeable sodium varies inversely with the body fat mass.[1] Therefore, referring exchangeable sodium to total body water rather than to body weight tends to lessen discrepancies resulting from inevitable variations in the body fat mass.

Sodium Space.—The sodium space, representing the volume of distribution of the injected radioactive sodium, is expressed as milliliters per kilogram of body weight. The mean value of 564 is almost twice the mean value seen in normal adults and reflects the markedly increased sodium stores in the newborn infant. Only a small number of determinations of sodium space have been made in the newborn period. These are shown in Table 2.

† References 3 and 4.

TABLE 2.—*Sodium Space in Newborn Infants*

Reference	Age	Cases	Sodium Space	Method
Perley, et al[14]	16 hr.	1	328	Na^{24}
	1 day	1	355	Na^{24}
	2 days	1	340	Na^{24}
Flexner, et al[14]	1.5 days	1	408	Na^{24}

The time interval between the time of injection and final determination of the sodium space using Na^{24} ranged from 1 hour 40 minutes to 3 hours 56 minutes. In the present study utilizing Na^{22}, 24 hours elapsed between the time of injection and final determination of the sodium space.

The results in our study of 17 newborns are consistently higher than previously reported values.

Total Body Water.—The values for total body water shown in Table 1 are appreciably lower than those found with use of deuterium oxide or antipyrine.

However, studies in newborns using a method of carcass desiccation and analysis closely correlate our findings.

Previous determinations of total body water in infants are as follows:

Values ranging between 59.4% and 72.9%, with an average of 66.2%, were found in the present study of 17 newborn infants under 42 hours of age, using 4-iodoantipyrine labeled with I^{131}.

The method of carcass desiccation and analysis yielded values between 66.4% and 79.6%, with an average of 71.8%, in a group of nine newborn infants.

In four premature infants, ranging in age from 15 days to 1 month, with use of deuterium oxide, values between 71.8% and 83.5%, with an average of 78.1%, were obtained. Also, in a group of five newborns, whose ages ranged from 1 to 7 days, studied with deuterium oxide, values between 73.2% and 78.9%, with an average of 76.1%, were obtained.

Two of the patients studied with deuterium were also given antipyrine. These patients were newborns, 1 to 3 days of age. The results were 78.7% and 79.7%, with an average of 79.2%.

One 15-day-old and one 16-day-old premature infant, previously studied with deuterium, were also given antipyrine. The results were 70.5% and 68.5%, respectively. Also, an additional 9-day-old premature was studied in the antipyrine group and the re-

TABLE 3.—*Total Body Water in Newborn Infants*

Reference	Age	Cases	H_2O % B.W.	Method
Widdowson[6]	Newborn	1	69.1	Desiccation
Bischoff[11]	Newborn	1	66.4	Desiccation
Fehling*	Newborn	1	74.0	Desiccation
Iob and Swanson[13]	Newborn	1	79.6	Desiccation
Camerer, et al[7]	Newborn	5	71.8 (av.) 71.6, 69.2, 73.0, 72.0, 72.0	Desiccation
Corsa, et al[8]	Premature (1 mo.)	1	83.3	D_2O
Friis-Hansen, et al[14]	Premature 15 days 16 days 21 days	3 1 1 1	76.2 (av.) 73.6 71.8 83.3	D_2O
Friis-Hansen, et al[14]	Newborn (1-3 days)	2	78.3 (av.) 77.6, 78.9	D_2O
Flexner, et al[14]	Newborn (1.5-7 days)	3	74.6 (av.) 73.8, 76.8, 73.2	D_2O
Friis-Hansen, et al[10]	Newborn (1-3 days, same pts. used for D_2O above)	2	79.2 (av.) 79.7, 78.7	Antipyrine
Friis-Hansen, et al[10]	Premature 9 days 15 days 16 days	3 1 1 1	72.3 (av.) 79.3 70.5 66.5	Antipyrine
Same pts. used for D_2O above				

* Fehling, H., cited by Shohl.[12]

sult was 79.3%. An average for this premature group was 72.3%.

Studies done on newborn rats by us, using direct chemical analysis for determining the total body water, resulted in values appreciably higher than seen in the newborn infants in our series.

Comment

The method of determination of total body water with the use of deuterium oxide or tritiated water is the most ideal method for determining body water. However, the equipment and instrumentation necessary for the determination are commonly beyond the means of many laboratories. The deuterium space is thought to be greater than total body water, owing to the fact that deuterium probably enters into equilibrium reactions with hydrogen other than that found in body water.

Antipyrine also has been used for the measurement of total body water; however, owing to large quantities of serum necessary for analyses, this method is not applicable to the newborn infant. With radioactive-labeled antipyrine this objection can be averted because of the relatively small quantities of blood required. The radioactive-labeled antipyrine compound has been compared with the standard antipyrine technique and has been found to compare satisfactorily.

In this newborn study, as well as in a previous study on a group of adults,[2] total body water was measured utilizing 4-iodo-antipyrine labeled with I^{131}. A very rapid urinary excretion of the substance (71% in 24 hours) makes the safety factor of reduced radiation hazard ideal for the newborn period.

There are several possible reasons for the discrepancies in the values for total body water.

First: The newborn infants in the present study are all in a complete state of fasting until eight hours after the time of injection of the isotopes. This resulted in a group of infants without fluid intake for a minimum of 14 hours and a maximum of 50 hours. This would undoubtedly produce a decrease of total body water.

Second: The body of a newborn infant contains an undetermined, but probably

variable, amount of fat. As a result, in babies with large fat stores total body water as related to body weight will be low in comparison with babies having smaller fat stores.

Third: There is a problem of equilibration of 4-iodoantipyrine; 4-iodoantipyrine distributes itself in a volume approximating body water and is reversibly bound to plasma and tissue protein.[6] The possibility of competitive protein binding may alter the distribution and equilibration and would result in a smaller apparent volume of distribution.

The small number of determinations made on newborn infants in the first 24 to 48 hours after birth is not sufficient to validate a statistical norm. Until such time as adequate numbers of patients are studied, only a range of normal can be proposed.

The serum sodium, as well as the exchangeable sodium, in our patients has shown consistently high measurements, thereby suggesting that the increased retention of sodium may be due to an increased adrenal cortical activity and is inversely proportional to the state of maturation rather than to size or age.

Summary

Total body water and exchangeable sodium were measured in 17 newborn infants. The mean value for total body water was 2.19 kg., or 66.2% of body weight. The mean value for exchangeable sodium was 283 mEq., or 86 mEq./kg. The mean value for sodium space was 564 ml/kg. B.W.

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Migraine in Childhood

A Preliminary Report

EDMUND C. BURKE, M.D.
and
GUSTAVUS A. PETERS, M.D., Rochester, Minn.

This is a report of a study of 92 cases in which a diagnosis of migraine was made in the Section of Pediatrics at the Mayo Clinic during the six-year period of Jan. 1, 1950, through Dec. 31, 1955. The study was undertaken to obtain information regarding the clinical features of migraine in childhood. We hoped to record data on sex distribution, age at onset, etiologic factors, and the comparative roles of allergic and psychogenic influences in migraine. Follow-up letters in the form of a questionnaire were mailed to the parents of 89 patients. The results and tabulation of this information will be presented.

Background

Migraine in adults is encountered in practice with regularity but we consider that migraine in childhood has been diagnosed infrequently and that the syndrome has been somewhat neglected.

Migraine may be defined as a syndrome characterized by headache, associated gastrointestinal disturbances, and visual complaints. This pattern recurs irregularly and with varying severity. The attacks may vary in the same patient, as well as from one patient to the next. The patient remains well between attacks, although each episode may be severe enough to incapacitate him for an entire 24-hour period. The occurrence of this syndrome in members of the same family and in several generations is common and probably significant.

One of us (Peters)[1] gave a figure of 10% as the incidence of migraine in adults. Reports of its occurrence in children vary widely. Glaser[2] found an incidence of approximately 1% in his pediatric practice and Ryan[3] placed his estimate at 2%.

Results

During the six-year period covered by this study of 92 cases, approximately 60,000 examinations occurred in the Section of Pediatrics, excluding those of newborn infants. Tabulation of data was dependent on facts elicited from the case records. Had some records been more nearly complete, additional weight might be given to the frequency of certain symptoms.

Table 1 presents some clinical data on

TABLE 1.—*Migraine in Childhood: Clinical Data in Ninety-Two Cases*

		Cases
Sex	Boys Girls	63 29
Age at onset, yr.	Range Average	1½-14 7.3
Electroencephalogram	Normal Abnormal	21 46
Headache	Frontal or orbital Other locations Location not specified	63 13 16
Nausea or vomiting or both		74
Visual manifestations	Scotomas Photophobia Blurred vision	9 23 9

Submitted for publication June 13, 1956.
Read before the Section of Pediatrics at the 105th Annual Meeting of the American Medical Association, Chicago, June 13, 1956.

Section of Pediatrics (Dr. Burke) and Section of Medicine (Dr. Peters), Mayo Clinic and Mayo Foundation. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

these 92 patients, of whom 63 were boys and 29 were girls, a ratio greater than 2:1. This is in surprising contrast to the sex distribution in migrainous adults, of whom 67% to 75% are women.[4]

The range in age at onset was from 1½ to 14 years, with an average of 7.3 years. In the series of Michael and Williams,[5] the average age at onset in 20 children was 6.9 years. Krupp and Friedman,[6] in a study of 50 children, did not give an average age at onset but did state that 35% experienced onset of symptoms before the fourth year of life. Approximately 17% of our patients were less than 5 years of age at the onset of symptoms.

Electroencephalograms were obtained from 67 children. A strikingly high incidence of abnormal tracings (46 instances) was noted. This is partly, though not entirely, accounted for by the presence of known and possibly latent convulsive disorders in the group. It also has to be remembered that 15% to 20% of the normal child population may show mild to moderate (grade 1 to 2) dysrhythmias. Bickford and one of us (Peters)* have noted a mild to moderate nonspecific type of dysrhythmia without localization in the electroencephalograms of a third of 100 adult patients who had migraine.

Frontal or orbital headaches were described by 63 children, while the headaches in 13 others were unilateral or, in several instances, occipital. The exact type and location of the headache were not specified in the other instances. The most distressing symptoms were nausea and vomiting, which were present in 74 patients. Nausea without vomiting was noted occasionally but it was unusual for these patients to have the typical headache without either of these accompanying symptoms.

Scotomas, which are common in migrainous attacks in adults, were uncommon in our patients. Only nine children described these symptoms and nine children complained of blurred vision. Other authors also have commented on the lower incidence of scotomas in children who have migraine as compared with migrainous adults.

TABLE 2.—*Migraine in Childhood: Further Clinical Data in Ninety-Two Cases*

	Cases
Family history of migraine	40
Associated neurologic features, such as convulsive disorders or hemiparesis	18
Pneumoencephalogram (all negative)	3
History of allergic manifestations	11
Migraine precipitated by tension, emotional upsets or exercise	26
Variants, such as abdominal migraine and auditory or tactile phenomena	9

Further data are summarized in Table 2. Positive histories of migraine in members of the immediate family and grandparents were obtained in 40 instances. Several children had been adopted and information regarding the parents could not be obtained. Stepparents were not subject to attacks of migraine in any instance.

Coexisting convulsive disorders were present in 7 of 18 children who had associated neurologic features, although the episodes of migraine in no way resembled the convulsive seizures. Nine of these eighteen children had numbness in the arms or hands, and one boy complained of a hissing sound in his ears during the headache. One had hemiplegia and three were mentally retarded. Expressive aphasia occurred in one child, and one had amnesia during the attacks. Another child, who had a meningocele repaired in infancy, had incomplete homonymous hemianopsia. One other child also had homonymous hemianopsia. Pneumoencephalograms were done on three children but in each instance the results were normal.

Histories of allergy were elicited from 11 children, 7 of whom had allergic rhinitis; one of the latter group also had bronchial asthma. No significant correlation was present between the allergic symptoms and attacks of migraine. Food allergy was noted in only two instances. One of these two

*Unpublished data.

children supposedly had had an allergy to milk in infancy; the second child reputedly had an allergy to pork, but results of cutaneous tests were negative. Two children had experienced attacks of angioneurotic edema.

In 26 children attacks of migraine definitely were associated with such precipitating factors as excitement, school examinations, family strife, a new dress, a trip to the barbershop, or other emotional factors. Physical exertion and fatigue also were precipitating factors. It was interesting, and undoubtedly significant, that the precipitating factor on occasions was thought to be television, movies, or bright sunshine.

Three of nine children whose conditions were classified as "variants" of migraine experienced episodes of pronounced and prolonged vomiting. Abdominal migraine was listed as the diagnosis in these children. One of these three had blurred vision with her abdominal attacks, as well as abnormal electroencephalographic changes. The second child also had an abnormal electroencephalogram and paraumbilical pain that was associated with a mild increase in temperature during each bout. The third child did not undergo electroencephalographic study, but her condition had been diagnosed previously as cyclic vomiting. Her father was subject to attacks of migraine. Cyclic vomiting has been considered closely allied to convulsive disorders and to migraine. In several authenticated instances, "cyclic vomiters" later experienced typical attacks of migraine.[7]

A fourth child in the category of "variants" was the aforementioned boy who experienced the hissing noise in his ears during the headaches. This boy also was listed in the group who had associated neurologic findings.

The remaining data are summarized in Table 3. The final diagnosis in six patients was "probable migraine." In reviewing the symptoms of these six patients, we considered that they had migraine, although only one or two attacks had been noted. Further evidence was the occurrence of migraine in the parents of some of these children in the "probable" category. This category also includes patients with headache that we refer to as the "migraine-tension" type. Of the three such patients encountered, two had abnormal electroencephalograms. The mother of the third child had typical attacks of migraine. This third child also had blurred vision with her headache but no nausea or vomiting. One of the two children with abnormal electroencephalograms also did not vomit, but his dysrhythmia arose from the posterior region of the head, the region commonly involved in patients who experience scotomas. The mother of this boy was subject to headaches of an indeterminate type.

TABLE 3.—*Migraine in Childhood: Further Clinical Data in Ninety-Two Cases*

	Cases
"Probable" migraine	6
Onset subsequent to illness or injury	11
Vascular phenomena (facial, temporal, or ophthalmic)	22
Migraine in morning	10
Migraine in afternoon	32

An antecedent illness or injury was noted in 11 patients; such factors as an auto accident, an ocular injury due to a snowball, a meningocele in infancy, an episode of lymphocytic choriomeningitis, and acute infantile hemiplegia were included.

Twenty-two children had manifested vascular changes about the temple or face. These were described at various times as a flushing of the face or temple, an ashen-gray pallor, or bloodshot eyes.

The majority (32) of the children from whom such information was available noted onset of the attacks in the afternoon. However, 10 of the records indicated the onset was in the morning. Either morning or afternoon episodes occurred in several instances.

It was not feasible to tabulate the frequency of occurrence of migrainous attacks because of their great variability. The frequency ranged from attacks nearly every

day to one every month or so. Likewise, we collected no data regarding the duration of the attacks. In the majority of children, recovery followed a night's sleep but the episodes lasted 36 to 48 hours in some of the children who had prolonged vomiting.

Comment

As the result of this study, we can hypothesize an average child who has migraine. The attack occurs in a 7-year-old boy who is nervous or emotionally labile and a good student. He suffers from headaches commencing in the afternoon, usually during the school months. This hypothetical patient comes into the house appearing rather pale and complaining of orbital or frontal headache. His mother gives him acetylsalicylic acid (aspirin) and puts him to bed in a darkened room because the light bothers him. He becomes nauseated and vomits many times. The emesis may last for only half an hour or it may continue into the evening. The child eventually falls asleep and sleeps until morning, when he awakens completely recovered. His mother has migrainous headaches about once a month except during pregnancy. This pattern in the average patient is repeated every two or three weeks but he may go through most of the summer without any distress.

It is important to mention briefly the physiologic aspect of this disorder, since it was shown to be a vascular disturbance by Wolff,[8] in 1948. Three phases occur in the syndrome of migraine. The initial phase is one of vasoconstriction of the intracranial arteries, during which time cortical phenomena, such as scotomas, hemianopsia, diplopia, paresthesia, and aphasia, may be noted by the patient. This phase is a short prodrome and may last only half an hour.

Headache heralds the onset of the second phase, which is produced by vasodilatation of intracranial vessels. In addition to the cephalgia, gastrointestinal symptoms, such as anorexia, nausea, and vomiting, are experienced. Dizziness and fever are occasionally noted, as well as frequent urination, perspiration, and palpitation. Sunlight, noises, and odors from cooking are likely to be disagreeable to the patient, who wishes to be left alone in a darkened room.

The third stage, that of edema, is less common, particularly in children. During this phase, pulsation of the temporal vessels, conjunctival suffusion, or flushing of the face may be observed.

Michael and Williams, in their aforementioned study of 20 children, noted that attacks were more frequent in this group than they were in adults. The onset occurred at the age of 2½ years in one of their patients. Vahlquist and Hackzell[9] reported on a one-year-old child who had attacks of migraine. Balyeat and Rinkel[10] had such a patient aged 1¼ years. Our series included a child aged 1½ years and another aged 2.

Comment should be made concerning the incidence of convulsive disorders in this group of migrainous children. We have mentioned previously that seven children in our series had convulsive disorders and also have referred to the large number (46) of abnormal electroencephalograms in the entire series. This significant association similarly has been observed by Michael and Williams, who also commented on the number of head injuries suffered by the children before the onset of migraine.

It is difficult to assess the significance of a history of head injury preceding the onset of migraine. In retrospect, parents are likely to recollect an illness or injury that antedated the migraine and that otherwise would have gone unnoted. Children in this age group are subject to frequent illnesses, many of them associated with severe fever, as well as to a high rate of accidents and head injuries.

Glaser, as well as a few other workers, has advanced the idea that allergy is a precipitating factor in migrainous attacks. We do not ascribe to this but consider that emotional stress, such as occurs during school and in family relationships, probably is more important in bringing about the attacks.[11]

Sensitivity to light may be present in some patients. We have seen convulsive seizures triggered by a flashing light, and a similar mechanism may operate in migrainous children.

Several important differences are evident between attacks of migraine in children and those in adults. The episodes occur more frequently in children. The headaches are less incapacitating than are the gastrointestinal symptoms in children. Scotomas, perspiration, vascular changes, and edema are less prominent in children.

Diagnosis

Headaches in youngsters of school age are at times perplexing problems in a pediatric practice. A minority of headaches in childhood undoubtedly are migrainous. The diagnosis, however, depends on the history.

The absence of neurologic signs, such as ataxia, diplopia, paralysis, and weakness, together with normal roentgenograms of the head and normal fundi usually rules out serious intracranial pathologic changes, such as tumors, effusion, or degenerative disease. It may be more difficult to separate migraine from the "tension" type of headache, since certain mixed forms of migraine are recognized. The electroencephalogram has proved helpful in some instances.

We have not seen histaminic cephalgia in children. This is an intensely painful headache of sudden onset and relatively short duration, associated with lacrimation and rhinorrhea.

Prognosis Based on the Questionnaire

As already indicated, letters were mailed to the parents of 89 children who had migraine, requesting information regarding the persistence, severity, and frequency of the attacks, the most efficacious drugs, and the known precipitating factors; 58 completed questionnaires were returned.

Table 4 summarizes information obtained from the questionnaires. The data are grouped by year to avoid the undesirable influence of facts obtained from the more numerous patients seen recently.

A total of 49 of 58 children still had migraine, whereas only 9 children no longer experienced attacks. Fewer headaches were admitted by 18 patients. Change in the severity of the headaches was not experienced by 17 patients, whereas less severe headaches were noted by 27; 5 children had severer headaches.

The age of each patient no longer experiencing attacks of migraine is given in Table 5. Each of these patients was in the adolescent group except for a 6-year-old boy who had obtained relief with diphenylhydantoin sodium (Dilantin). In the hope that we could demonstrate a commonly expressed belief that children "outgrow" migraine, we determined the number of children 15 years or more in each group classified by year who still had migraine. These data are given in Table 5. No significance can be attached to the greater age of the patients without headaches in view of the number of older children who still had migraine. However,

TABLE 4.—*Migraine in Childhood: Data from Questionnaire Sent to Eighty-Nine Children with Migraine*

	1950	1951	1952	1953	1954	1955	Total
Questionnaires*	16/9	13/7	10/6	7/7	20/12	23/17	89/58
Headaches still present	8	5	5	7	8	16	49
No headaches	1	2	1	0	4	1	9
Fewer headaches	2	1	2	2	5	6	18
Headaches of same severity	4	3	2	2	2	4	17
Headaches of less severity	4	2	2	5	4	10	27
Headaches of more severity	0	0	1	0	2	2	5

*The first number indicates total questionnaires sent and the second number indicates total received.

TABLE 5.—*Migraine in Childhood: Data from Questionnaire Sent to Eighty-Nine Children with Migraine*

	1950	1951	1952	1953	1954	1955
Ages (yr.) of patients who no longer had migraine	16	18, 17	15	...	16, 16, 17, 13	6
Patients aged 15 yr. or more still having migraine*	5 (6)	4 (5)	1 (5)	2 (7)	1 (8)	1 (16)
Patients aged 15 yr. or more having less severe migraine	4	1	0	0	0	1

*Numbers in parentheses indicate total number of children in each group still having migraine.

some of these older children had less severe migraine, as noted in this table.

On the basis of this small short-term follow-up, we are unable to furnish evidence that children who have migraine cease to be so afflicted as they proceed to adulthood.

Balyeat and Rinkel stated that 30% of their adult migrainous patients had experienced the onset of migraine in childhood. Ryan has expressed the opinion that headaches cease spontaneously at puberty in some patients. We hope to be able to furnish evidence from a subsequent long-term study as to the persistence or disappearance of migraine of childhood.

The parents of a total of 35 children indicated that emotional or physical exertion or both and, in some instances, movies, sunlight, or television were the provoking stimuli for attacks of migraine.

The quest for information regarding the efficacy of drugs was disappointing. The results could not be tabulated because of the numerous and varying types of treatment employed for relief.

Thus, the questionnaire did not reveal much information except that the majority of these children still had attacks of migraine and no single drug was outstandingly effectual.

Treatment

For relief of the attack, we consider that acetylsalicylic acid is probably the best agent for children if it can be administered in a sizable dose (1 grain [0.065 gm.] per year of age when given orally or 2 grains [0.13 gm.] per year when given rectally) early in the attack. Suppositories containing acetylsalicylic acid are now available for use when vomiting already has commenced. A combination of ergotamine tartrate and caffeine (Cafergot) given orally or in the form of rectal suppositories may be tried. This is an effective preparation in adults but less so in children.

In view of the irregularities in the electroencephalogram and the high incidence of convulsive disorders, we suggest that one of the anticonvulsant drugs be administered as a prophylactic measure. Diphenylhydantoin sodium in doses of ¾ grain to 1½ grains (50 to 100 mg.) or mephobarbital (Mebaral) in doses of ½ grain given once or twice daily may be tried. In the past year, a few encouraging results have been noted after adequate use of diphenylhydantoin sodium. Significant developments will be reported in the future.

Other observers have suggested the use of antihistaminic agents and the elimination of food offenders if they can be found, but this program has appeared to be less effective. Correction of any refractive errors and also any ear, nose, and throat problems, for example sinus problems, also is important.

Thorough understanding by the parents and the patient of the nature of the disorder, together with knowledge of the precipitating factors, appears essential. It is often helpful for the mother to keep a diary of the frequency and description of the episodes, as well as an account of the precipitating factors.

For most patients, considerable diligence on the part of the physician is required

before much progress can be made toward relief of this distressing illness. When dealing with migrainous children, it is common to discover that a considerable degree of parental pressure has been exerted on the child to excel in school. These children also are likely to have a full schedule of extracurricular activities, such as music or dancing lessons. The physician should point out such undesirable influences to the family.

Summary

A preliminary study has been made on 92 children who had migraine and who were encountered at the Mayo Clinic during a six-year period.

Migraine occurs oftener in childhood than has been appreciated. Children with migraine have scotomas less frequently than do adults who have migraine. They also have less cephalgia but more gastrointestinal symptoms than do similarly afflicted adults. The migrainous child has attacks more frequently than does the adult with migraine. Boys were more commonly affected than girls in this study.

Migraine is a vascular phenomenon of unknown cause. Psychogenic factors appear to play the greatest role in precipitating attacks. Elimination of these precipitating factors and an understanding of the mechanism of the attacks are essential to patient and parents. The study of migraine is complicated because of numerous functional aspects in the headaches of these children as a group.

The prognosis for disappearance of attacks cannot be given with statistical proof at this time. Additional studies concerning this aspect of the problem are indicated.

Administration of acetylsalicylic acid (aspirin) and a combination of ergotamine tartrate and caffeine (Cafergot), as well as use of diphenylhydantoin sodium (Dilantin), has been recommended. A suggestion is made for a trial of anticonvulsant drugs in adequate doses as a prophylactic measure.

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Epiphysiolysis

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The sharp limitation of the occurrence of slipping of the upper femoral epiphysis to the accelerative phase of the pubertal growth spurt, such variations as occur duplicating strikingly a frequency curve of the time of occurrence of the "year of maximum growth—the MG year"[1] (Fig. 1), suggests

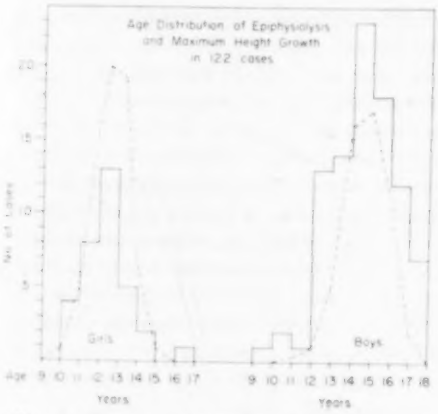

Fig. 1.—The age distribution of 122 cases of epiphysiolysis, 32 females and 92 males, is plotted with solid line above. The age distribution of the "MG-year" is indicated by the dotted line (Reference 1). The similarity of the two curves emphasizes the intimate relationship between rapid growth and epiphysiolysis.

conditioning of the episode by a metabolic abnormality peculiar to this period. The fact that it occurs most frequently in the overweight child recalls an old observation of a reciprocal relationship between gain in weight and calcium retention[2]; the more rapidly the growing animal was permitted to gain in weight, the more florid the rickets that resulted from the Steenbock diet. A similar phenomenon is observed when testosterone is administered to the normal boy; marked increase in the retention of nitrogen is accompanied by reciprocal fall in calcium storage.[3] It is the thesis of this paper that suboptimal mineralization is occurring in the child with the slipped upper femoral epiphysis, that a number of factors may contribute to this, and that in his role as supervisor of the growth process the pediatrician may make a preventive contribution by an awareness of the potentiality of its occurrence in the years that precede its anticipated incidence.

Key[4] in 1926 published his classic review of the subject and discussed in detail the theories regarding etiology — osteomalacia, juvenile rickets, chondrodystrophy, low-grade infection at the site of the lesion, mechanical stress on the epiphyseal line with its peculiar anatomical situation, trauma, and poorly defined endocrine disorders associated with the onset of puberty. He felt that none of these theories provided a satisfactory explanation for the disorder and proposed instead two factors which he felt provided a better explanation. The first factor was the observation that the periosteum in childhood was thick and strong but became thin and relatively atrophic in adulthood. Experimentally, and with fresh bone specimens, it had been shown that only one-fifth as much force is necessary to displace the capital femoral epiphysis if the periosteum is first removed. This he felt suggested that the transition from childhood to adult-type periosteum played a role in the slipping. The

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From the Department of Pediatrics and the Division of Orthopedics, Henry Ford Hospital. Balance determinations were supervised by Dr. O. H. Gaebler, of the Edsel B. Ford Institute for Medical Research, and were performed by Lois Beers, B.S., and Rosemary Holland, B.S. Mrs. Wertz supervised the diets and Miss Edna Jahraus the calculations.

second factor was the period of rapid growth which immediately preceded the slipping and which was felt to aggravate the periosteal transition by stretching and thinning the tissue to the point of weakness.

Most of the above etiologic theories have not stood the test of time. Some certainly play a role in the pathogenesis of the disease. None provides an adequate explanation of the disease process. This age period is one characterized by doubling of the rate of skeletal growth, proportionately greater in the extremities than in the trunk, and by profound endocrine changes incident to sexual maturation. That these latter may play a role in the production of epiphysiolysis is suggested (1) by the tendency for adolescents who acquire it to be larger than others of the same age, and (2) by the similarity in the widening of the epiphyseal line, considered to be a forerunner to the actual slipping to that produced in rats by the administration of pituitary growth substance.[5] The plotting of 20 of our cases on the Wetzel grid illustrates the first point (Fig. 2). However, we know of no evidence that these children, aside from their size, show other evidence of endocrinopathy.

Pathology

Pathological studies of operative specimens have not been helpful in elucidating the pathogenesis of the disease. There are reported only cases in which the slipping has already occurred and therefore represent far-advanced disease, often with the histological changes of secondary healing processes obscuring the original pathology.* Howorth[8] has described three stages in the pathology of epiphysiolysis: the preslipping stage, the slipping stage, and the residual stage. He records in the preslipping stage a swollen synovial membrane, hyperemic and showing villous formation. There is perivascular infiltration, and similar milder changes are seen in the periosteum and joint capsule. In the slipping stage he describes separation between the neck and the epiphyseal disc, in some cases suggesting avulsion. The head remains attached to the neck by soft tissues, however. The cellular infiltration is seen to only a very minor degree. Subsequent pathologic changes are those of degeneration and repair, incident to the slipping itself. The most recent report of the pathology of the disease is by LaCroix and Verbrugge,[9] who studied operative specimens from cases three years after the slipping had occurred and found osteoclasis in the subperiosteal area on the superior aspect of the femoral neck and adjacent to the upper part of the head. At the junction of the lower aspect of the neck and the displaced head, they found areas of spotty osteoblastic activity with islands of new bone in an area of fibrous tissue. They did not believe that this latter contributed much to the strength of the bone. In the area between these two points they observed an area of cartilage undergoing fibrillar degenerative changes and transformation into fibrous tissue. These workers felt that their studies demonstrated that the disease was due to a failure of endochondral bone formation. Considered critically, it would appear that the changes they describe in all probability represent simply the effort of the tissues inolved to heal after the slipping has occurred rather than the pathology of the primary disease process. Clearly the pathology of epiphysiolysis differs markedly from that of rickets.[10]

Harris [11] has reported experimental pathological studies which suggest an endocrine basis for slipping of the upper femoral epiphysis. Rats were used in this study; one group was given a growth-hormone preparation and a second group given estrogens. The amount of force necessary to separate the proximal tibial epiphysis of the isolated bone was measured and compared with a control group of animals. Approximately half as much force was necessary to separate the epiphysis in the group which had received the growth hormone compared with the normal controls, while twice as much force was necessary to separate the epiphyses in the estrogen-treated group. Micro-

* References 6 and 7.

scopically the separation was seen to occur in all groups in a proliferating layer of cartilage cells in the epiphyseal plate. It was shown that in the growth-hormone-treated group this layer of proliferating cartilage was abnormally thick, while in the estrogen treated group the same layer was thinner than in the control group.

The critical difference, then, was the thickness of the uncalcified epiphyseal plate, the thicker plate being much more amenable to separation than the normal controls or the estrogen-treated groups. It was felt that the growth-hormone preparation directly stimulated epiphyseal-cell proliferation, while estrogen depressed cell proliferation by suppressing endogenous pituitary growth-hormone elaboration. Harris notes the classic observation that epiphysiolysis occurs in children with two diffierent types of body habitus, the tall thin child and the large obese child. He feels his observations suggest that in the former there is an excess of growth hormone relative to sex hormone, while in the latter type there is a deficiency of sex hormone relative to the growth hormone. Expressed another way, there was a deficiency of sex hormones relative to the growth hormone in either case. Estrogen was used in the study as a representative sex hormone because its inhibitory effect on the anterior pituitary was better known.

Etiological Studies

The basic problem in determining the etiology of epiphysiolysis resolves itself, them, to ascertaining what factor or factors are responsible for the thickened, weakened epiphyseal plate in these children. It seemed to us that if excessive weight gain and growth could be controlled and proper mineralization of the epiphyseal plate ensured, the slipping itself might be averted almost regardless of the basic etiology. In a series of studies, we have been attempting to develop the thesis that suboptimal mineralization might result from many different causes and that it is possible that no single one is at fault as the underlying cause of epiphysiolysis. Among the causes are (1) the inadequacy of the intake of calcium and of vitamin D, (2) disproportionate gain in weight, (3) interference with calcium utilization resulting from infection, and (4) hormonal influences. Other disorders impairing calcium metabolism, such as chronic renal disease, parathyroid disease, and liver disease, are not pertinent to the present discussion.

1. *Intake.*—There would seem to be wide latitude in the calcium requirement of the growing child, except in those periods when growth rate is accelerated. Previous studies [12] have shown that in the accelerative phase of the pubertal growth period, during which epiphysiolysis is encountered, there is a definite need for about 1300 mg. of calcium daily and that an added source of vitamin D is essential, preferably about 1000 I. U. In several instances here reported, dietary history revealed an inadequate calcium intake and failure to use supplementary vitamin D. On the patient's discharge from the hospital after nailing, high intakes of calcium and vitamin D were prescribed, and it is possible that these contributed to the failure of postoperative aseptic necrosis of the femoral head—so commonly encountered in other reports—to occur in our series.

2. *Disproportionate Weight Gain.*—When weight gain occurs which is disproportionate to gain in height, a situation deleterious to optimal bone mineralization arises. The calcium requirement of the individual rises, as does the vitamin-D requirement. The situation is reminiscent of that seen in dogs on the Steenbock diet: i. e., rickets is not seen if growth is inhibited by holding food intake at low level, whereas if growth occurs rickets soon becomes apparent. Excessive weight gain also has the adverse quality of usually implying marginal protein and excessive carbohydrate intake which provides the obese person with a poor metabolic mixture.

3. *Infection.*—Stieda [13] in 1901 appears to have been the first to have observed chronic infection as a possible etiologic fac-

tor in this disease. However, chronic infection is not found in all, or indeed in many of the reported cases. Yet it remains of considerable interest as a contributing factor because of its depressing effect on calcium absorption. The following balance study on a child receiving a constant diet who had chronically infected tonsils and adenoids illustrates this point:

	Calcium Retention	Nitrogen Retention
18-day control period	0.069 gm./day	0.43 gm./day
18-day period after adenotonsillectomy	0.210 gm./day	1.24 gm./day

In two instances in our series the condition developed after an acute febrile illness, three had chronically infected tonsils, one granular pharyngitis, one sinusitis. In most instances the children were unusually healthy, except for obesity.

	Nitrogen Balance	Calcium Balance
18 day control period	−0.21 gm./day	+0.268 gm./day
18 day Antuitrin G period	+0.63 gm./day	−0.033 gm./day

4. *Hormonal Influence.*—The probable role of the pituitary in the development of epiphysiolysis is emphasized in the previously noted experimental study by Harris. In a balance study on an 18-year-old girl reported earlier, we observed conversion of a positive to a negative calcium balance following the administration of growth-hormone preparation (Antuitrin G). We had previously shown that this preparation produced increased nitrogen retention in a period of growth.[14] Whether this catabolic effect in reference to calcium was due to the fact that this child had passed the growth period we cannot say. The data on this study were as follows:

This study strongly suggests that the growth hormone itself has a deleterious effect on calcium retention and, if Harris' observations in experimental animals are applicable to human adolescents, then the patient with the preslipping phase of epiphysiolysis has an additional factor in ante-

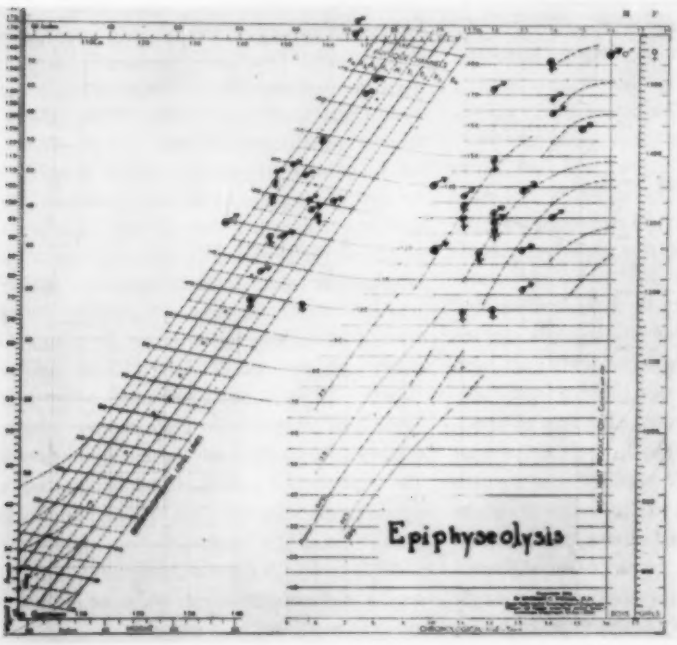

Fig. 2.—Plotting of 20 unselected cases of epiphysiolysis on the Wetzel grid illustrates the tendency for these patients to be taller and heavier than their contemporaries.

rior pituitary hyperfunction tending to impair his storage of calcium. Furthermore, the obese somatotype associated with epiphysiolysis often fulfills the criteria of functional hyperpituitarism as described by Talbot and co-workers.[15]

That the thyroid is not at fault would seem reasonably certain. Neither hypo- nor hyperactivity of this gland is compatible with normal storage of calcium in the growth period. Metabolic rates of 15 of our patients show a low rate when actual surface area is used as a standard of surface area; however, when correction is made for the obesity which they often show by use of a standard based on height or on the Wetzel grid, the metabolic rates are for the most part slightly elevated. One instance is noted in which the unwise use of large doses of thyroid extract for the control of obesity preceded the slipping, and it is possible that this may have played a role in demineralization.

Excessive amounts of both androgens [3] and estrogens [16] administered at this age will reduce calcium storage, but Harris' work suggests that it is a relative deficiency of sex hormones in the case of either somatotype usually affected with the disease which results in the weakness of the epiphyseal plate and subsequent slipping. Excessive sex-hormone secretion would therefore not seem to be a factor in the pathogenesis of the disease.

Methods

Continuous balance studies on nitrogen and calcium, with periodic determinations of the basal metabolic rate, were carried out in the manner described in detail in reports of previous studies.† Periods of 18 days were used, since this represented in the case of calcium the minimum number of days which could be considered statistically significant. At the time the balance studies were done, all patients enjoyed approximately the same level of activity, that is, they were either up about the ward in a wheel chair or ambulatory on crutches. Four had nailing done at least five days previously. One, Case No. 2, had not been treated surgically on the present admission but had been in traction for 24 hours 3 days prior to the beginning of the balance studies. The percomorph liver oil used contained 180 I. U. vitamin D per drop. The irradiated ergosterol (viosterol) contained 200 to 220 I. U. vitamin D per drop.

† References 17 and 18.

Clinical Summaries

Case 1.—A 14-year-old boy who gained 5 in. of height from October, 1946, to October, 1947. A limp appeared in the spring of 1947. Nailing was done Oct. 15; he was in a wheel chair on the Oct. 19 and walked on crutches Oct. 21. Balance study began Oct. 27 and lasted 36 days.

Case 2.—A 12-year-old girl had been operated on nine months previously on one side and was hospitalized with symptoms referable to the other side. On June 28, 1940, she was placed in traction for 24 hours, and on June 29, while still a bed patient, exercises were begun in the Hubbard tank. She began using a wheelchair on July 4, and on July 9 she began walking without crutches. Balance study extended from July 1 to Aug. 8, 1940.

Case 3.—An 11-year-old girl, underwent nailing on Nov. 11, 1939. She attended the hospital school on Nov. 20 and rode a stationary bicycle on Nov. 27. Balance study extended from Nov. 15 to Dec. 20, 1947.

Case 4.—An 11-year-old girl developed symptoms referable to the left hip following a mild injury six months previously. In the two months before admission symptoms became worse. The patient was placed in skin traction for several days, after which she was placed on crutches and unlimited activity for the duration of the balance study and prior to nailing. Balance study extended from Oct. 11, to Nov. 11, 1948.

Case 5.—A 14-year-old boy developed left-sided limp in February, 1947, after a baseball game. Diagnosis of epiphysiolysis was made at another hospital, and the boy was referred to this hospital for treatment. He had had no supplementary vitamin D for years, though he did receive a quart of milk daily. After bed rest and skin traction to the affected hip for several days, the boy was allowed unlimited activity on crutches for the duration of the balance study. This extended from July 14 to 31, 1947. Nailing was done on Aug. 6, 1947. Only a control balance period of 18 days was done on this boy, since parental disinclination precluded further study.

Case 6.—A 13-year-old boy developed symptoms referable to the hip following injury. Nailing was done Aug. 29, 1946. Exercise began in a Hubbard tank Sept. 11, and he began using a wheel chair on Sept. 13 and continued to receive daily physical therapy. Balance study extended from Sept. 21 through Oct. 26, 1946.

Case 7.—A 14-year-old boy underwent nailing of the affected hip on Sept. 10, 1945. This was followed by temperature elevation for 10 days

TABLE 1.—*Balance Data*

Case	Date	Nitrogen					Calcium					BMR						
		Urine	Stool	Output	Intake	Balance	Urine	Stool	Output	Intake	Balance	B.	W.	RQ	Total Cals.	Wgt.	Hgt.	Rx
1	10/27 to 11/13	12.03	1.42	13.45	15.10	+1.65	0.259	1.066	1.325	1.311	−0.014	−14	±0	0.74	1560	133	64	
	11/14 to 12/1	12.49	1.46	13.95	15.28	+1.33	0.120	1.078	1.198	1.399	+0.201	− 6	±0	0.78	1542			Oleum percomorph
2	7/1 to 7/17	12.81	0.99	13.78	13.82	+0.04	0.184	0.851	1.035	1.210	+0.175	− 5	−1	0.81	1350	104	62	
	7/18 to 8/4	11.21	1.04	12.25	14.15	+1.90	0.153	0.711	0.864	1.232	+0.368	− 5	+3	0.77	1407	105	62	Viosterol gtt. VIII
3	11/15 to 12/2	10.87	1.11	11.98	12.74	+0.76	0.319	0.987	1.305	1.266	−0.039		−2	0.76	1317	87	58	
	12/3 to 12/14	9.77	1.15	10.92	12.44	+1.54	0.159	0.960	1.119	1.240	+0.156	− 1	+4	0.79	1369	87	60	Viosterol gtt. VIII
4	10/11 to 10/28	11.62	1.08	12.70	14.58	+1.88	0.169	1.000	1.169	1.232	+0.063	− 4	+9	0.78	1390	93	60	
	10/29 to 11/15	12.37	0.98	13.35	13.92	+0.57	0.146	0.901	1.047	1.186	+0.183	−14	±0	0.79	1262	94	61	Vit. D 1000 U.
5	7/14 to 7/31	9.21	1.68	10.99	13.61	+1.45	0.089	0.701	0.790	1.202	+0.412	−11	+0	0.74	1624	148	61	Control only
6	9/4 to 10/8	8.47	1.01	9.48	12.16	+2.68	0.196	0.852	1.048	1.161	+0.113	−16	−12	0.76	1119	78	58	
	10/9 to 10/26	8.81	1.48	10.29	13.55	+3.26	0.99	1.075	1.174	1.151	−0.023	−13	−8	0.76	1200	81	58	Thyroid 30 mg/day
7	9/21 to 10/8	9.96	1.16	11.12	14.84	+3.72	0.241	1.072	1.313	1.399	+0.086	−15	+2	0.75	1688	146	68	
	10/9 to 10/26	8.84	1.25	10.09	15.07	+4.98	0.133	1.159	1.292	1.284	−0.007	− 8	+10	0.76	1829	149	68	10 mg. testosterone

postoperatively. Physical therapy began Oct. 1, and the boy used crutches from Oct. 11 on. Balance study extended from Sept. 21 to Oct. 26, 1945.

Balance Findings

The balance findings are tabulated in Table 1. It will be seen that all of the balances are either negative or, if positive, show retentions considerably less than we have recorded elsewhere for this age group [19]

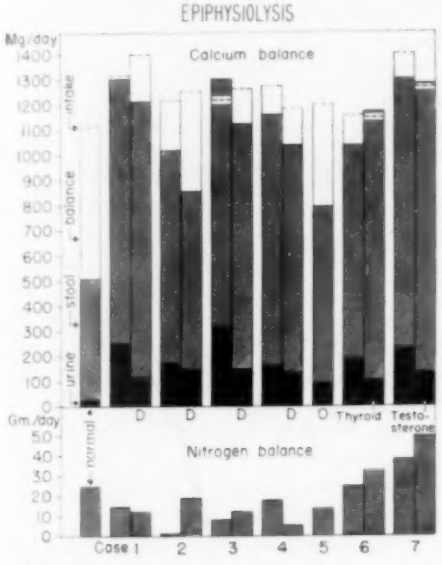

Fig. 3.—Balances for nitrogen and calcium obtained in seven epiphysiolysis patients compared with the normal child of comparable age. Note that all of the calcium retentions are less than found in the normal child and that Case 3 shows a negative calcium balance, evidence of disturbed calcium and phosphorus metabolism.

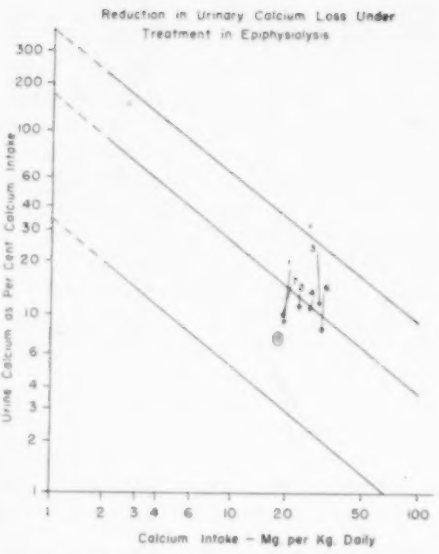
Reduction in Urinary Calcium Loss Under Treatment in Epiphysiolysis
Urine Calcium as Per Cent Calcium Intake
Calcium Intake — Mg. per Kg. Daily

Fig. 4.—Urinary calcium excretion in epiphysiolysis patients before and after therapy. These data are plotted on the curves reported by Knapp (Reference 20), and her mean and ±1. S. D. are indicated by the parallel diagonal lines above. While vitamin D, testosterone, and thyroid extract all produced reduction of urinary calcium excretion, it is emphasized that the balance studies showed net increase in calcium retention only with vitamin D.

(Fig. 3). Also, it will be noted that the use of vitamin D frankly improved the retention of calcium, though not in the way usually seen in rickets, but largely by reduction in urinary loss. However, in three out of four instances fecal loss declined also. In Figure 4 we have plotted the range of urinary calcium excretion in normal persons as reported

TABLE 2.—*Daily Calcium Data*

Patient	Kg. Weight	Calcium Intake, Mg.		Calcium Intake per Kg. Weight		Urine Ca × 100 / Intake Ca		Treatment
		Control	Treatment	Control	Treatment	Control	Treatment	
1	61	1311	1309	21	23	20	8.6	Vitamin D
2	48	1210	1232	25	26	15	12	Vitamin D
3	39	1266	1240	30	32	25	13	Vitamin D
4	42	1232	1186	29	28	14	12	Vitamin D
5	67	1202	...	18	..	74	..	Control only
6	35	1161	1151	33	33	17	8.6	Thyroid extract
7	67	1309	1284	21	19	17	10	Methyl testosterone

by Knapp[20] and indicated the degree of diminished urinary calcium excretion in our patients following vitamin-D dosage. These figures are also tabulated in Table 2 together with the patients' body weight and data on their total daily calcium intake, which shows minimal variation of 1151 to 1399 mg. per day. This represents the calcium present in one quart of average milk. Further evidence that epiphysiolysis is a consequence of disturbed calcium and phosphorus metabolism and might be expected to respond to vitamin-D administration is to be found in comparing serum phosphorus levels in our patients with the range of normal for their respective ages, as reported by Bullock.[21] Figure 5 illustrates the range of normal for certain ages, and the levels obtained in six of our balance subjects are plotted together with levels obtained in five other epiphysiolysis patients who were not studied by balance methods. It will be noted that 4 of the 11 patients fall below the normal range, while the remaining 7 are all within the lower limits of normal. The serum calcium in these patients was in excess of 10.4 mg. per 100 cc., except for one case in which it was 9.6 mg. per 100 cc.

SERUM INORGANIC PHOSPHORUS LEVELS IN EPIPHYSIOLYSIS COMPARED BY AGE WITH NORMAL RANGE

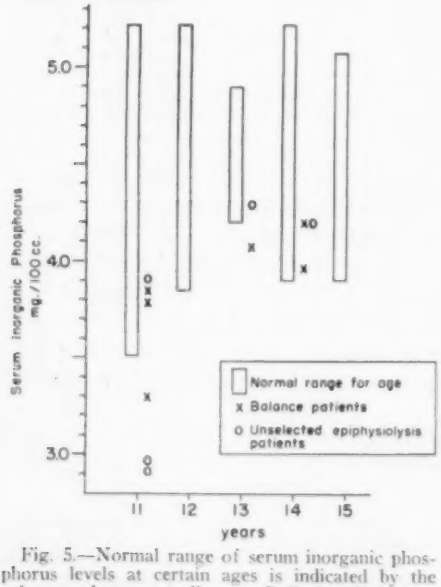

Fig. 5.—Normal range of serum inorganic phosphorus levels at certain ages is indicated by the columns above according to Bullock (Reference 21). Circles indicate random serum phosphorus determinations on some of our epiphysiolysis patients, while crosses indicate determinations on six of the seven patients whose balance studies are reported here. All of these patients show serum inorganic phosphorus levels at or below the lower limits of normal for their respective ages, further evidence of disturbed calcium and phosphorus metabolism.

The use of testosterone in one boy was frankly experimental and was followed by increased nitrogen retention but a further reduction in his already minimal calcium retention. This has been previously discussed.[3] The catabolic effect of thyroid extract in reference to calcium in W. S. is not entirely clear. We felt that this patient showed a low metabolic rate; yet, if this were so, the dosage of thyroid extract given might have been expected to increase calcium retention by way of decreased fecal loss. That the boy showed increased fecal and urinary losses of calcium suggests that he was actually euthyroid and that the thyroid extract given produced actual demineralization which we have previously reported.‡ An alternative explanation may be that the observation was not continued long enough for the anabolic effect of thyroid extract at this dosage level to be recorded.

Two factors having a critical effect on nitrogen and calcium balance we have attempted to control in this study. These are the effects of the postoperative state and resumption of activity on nitrogen and calcium retention. Howard and associates[22] studied the urinary excretion of calcium and phosphorus in patients convalescent from fracture and osteotomy, including four patients with epiphysiolysis who were subjected to femoral osteotomy, and found abnormal urinary losses of calcium and nitrogen persisting as long as 70 days in some instances. In all but a few instances these losses did not begin to fall until activity was begun. In no case did large doses of vitamin D influence the urinary loss of calcium. All cases were at bed rest

‡ References 17 and 18.

and immobilized with full-length leg cast and often with partial body cast. In the present series, three patients (cases 2, 4, and 5) were not in the postoperative state. Six of these patients were ambulatory on crutches; one was in a wheel chair and receiving physical therapy. In those patients treated surgically, all began balance studies 5 to 12 days postoperatively. In analyzing the vitamin-D-treated group it is seen that there is no significant difference in the effect on calcium balance in those patients operated on compared with those not operated on. We believe, therefore, that this excludes resumption of activity on metabolic recovery from surgery as explanations for the favorable effect on calcium balance observed after the administration of vitamin D.

Comment

The pathogenesis of epiphysiolysis remains incompletely known. Undoubtedly, Key's concept of periosteal thinning occurring during the puberty growth period plays a role in the weakness of the epiphyseal plate but a minor one. Other factors, such as the anatomically unique situation of the upper femoral epiphysis, certainly contribute to final slipping. However, the basic problem of what causes the thickening and weakness of the epiphysis has not been solved. Presently, the theory which seems to fit best the clinical picture of the disease is that of Harris, which suggests that the thickened weak epiphyseal plate is a consequence of a relative deficiency of sex hormones referable to pituitary growth hormone. This theory at least provides a rationale for preventive therapy.

Subjected to metabolic balance studies, all our subjects showed subnormal calcium retention for their ages. In four instances in which vitamin D was given, marked improvement in calcium retention resulted. Probably the low calcium retention was not due to the postoperative state, for it was improved by vitamin-D dosage. These balance-study figures suggest that suboptimal mineralization plays a role in the causation of epiphysiolysis. Analysis of serum phosphorus levels corroborate this. The favorable balances obtained with adequate calcium and vitamin-D intake immediately suggest one approach to prevention of the disease. The patient in the accelerative phase of puberty growth requires 1300-1400 mg. of calcium and 1000 I. U. of vitamin D daily to ensure optimal mineralization.

Preventive care directed at the obese older child who may develop the disease in a few years is equally well defined. Dietary habits should be reviewed and the high-carbohydrate, low-protein diets usually seen in these children corrected. A protein intake representing 20% of the total caloric intake is essential if total calories are reduced, together with the amount of calcium found in a quart of milk and approximately 1000 units of vitamin D daily. Occasionally one sees an obese patient whose only dietary error is excessive consumption of food of proper caloric distribution, and here the method of management is clear. It is emphasized that children who by reason of body habitus, familial growth pattern, or dietary indiscretion are obese or becoming so should be detected early and appropriate preventive measures taken. If not detected and given preventive care early, one can not expect to control obesity in the last year before the onset of the prepuberty growth spurt.

The rapidly growing tall, thin child presents a somewhat different problem. If such a child develops epiphysiolysis because of relative excess of growth hormone relative to sex hormones, logically treatment with sex hormones seems indicated. However, such an approach has several disadvantages: Testosterone and estrogen produce decreased calcium retention,§ epiphyseal closure before completion of normal growth is likely, and the orderly progression of endocrine devolpment in prepubertile children is interfered with. Prophylactic sex-hormone therapy would seem contraindicated at the present time. Its use after slipping has occurred on one side to effect closure and reduce the

§ References 2 and 15.

chance of slipping of the other hip seems rational and is under study by the orthopedists. On the basis of the results of the previous balance studies, the preventive treatment of choice in this somatotype is the provision of an adequate diet deriving 20% of the calories from protein and the meticulous day-to-day ingestion of adequate calcium, phosphorus, and vitamin D. The latter is especially important and should be continued until two years after the attainment of sexual maturity at which time bone growth will have ceased.

Summary

The pathogenesis of epiphysiolysis is reviewed and the theory most tenable on the basis of studies to date discussed.

Seven balance studies on epiphysiolysis patients are presented, six of which show subnormal calcium retentions and serum phosphorus levels.

In four cases in which it was employed, adequate vitamin D is shown to increase calcium retention significantly.

The concept that epiphysiolysis is a disease preventable by proper nutritional practice is emphasized and specified dietary regimens are suggested.

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Cystic Fibrosis of the Pancreas with Varying Degrees of Pancreatic Insufficiency

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The diagnosis of cystic fibrosis of the pancreas rests upon characteristic laboratory findings. In the past, the most reliable test was based on a study of the duodenal aspirate for pancreatic enzyme activity. The absence or marked diminution of tryptic activity in the duodenal aspirate in childhood was considered pathognomonic of cystic fibrosis of the pancreas, with rare exception. Conversely, the presence of tryptic activity was considered sufficient evidence to discard this diagnosis. The exact end-point of tryptic activity for this differentiation has always been difficult to define. Most observers drew the line of demarcation at tryptic activity less than 10% of normal. As a result of a large clinical experience coupled with an active and continuous interest in the development of better diagnostic methods, we feel a need for broadening the so-called classical criteria for the diagnosis of cystic fibrosis. As early as 1947 we had evidence that this disease does not present itself in an "all or none" manner insofar as the pancreas is concerned. It was unorthodox at that time to suggest that a patient might actually succumb with cystic fibrosis and show normal or nearly normal proteolytic activity of the duodenal fluid during life. We are now able to state that a number of patients with cystic fibrosis of the pancreas may show no clinical or laboratory features of pancreatic enzyme deficiency when first observed. As the pancreatic lesion progresses, clinical and laboratory features of pancreatic enzyme deficiency appear. The progression to complete pancreatic insufficiency may take months or years. In the meantime, the patient may succumb as a result of an extensive pulmonary infection. The frequency with which partial pancreatic insufficiency occurs is unknown. This is not a rare or an exceptional event, as indicated by our estimate of a 10% to 15% incidence in approximately 500 patients with cystic fibrosis studied during the past nine years. Our observations and conclusions are supported by the work of Gibbs and coworkers [1] and di Sant'Agnese.[2]

The purpose of this paper is to present our clinical and laboratory observations in a group of patients having cystic fibrosis in whom partial or incomplete pancreatic insufficiency was a feature. In each case the duodenal fluid, when first examined, showed normal or near-normal proteolytic activity. The pulmonary manifestations of the disease preceded and overshadowed the symptoms and laboratory evidence of pancreatic insufficiency. Our observations on the progressive involvement of the pancreas in a selected number of patients will be shown. The results of the sweat electrolyte concentration following a mild thermal stimulus will be given. We shall point out the fallacy of the trypsin measurement as the sole yardstick of pancreatic function.

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Before proceeding with the case material we should like to present our view concerning nomenclature. To call this disease a disease of the pancreas or a cystic disease is truly erroneous. In order to present a clearer picture of this *generalized disease* Farber in 1945 introduced the name "mucoviscidosis" as a temporary convenience.[3] Inasmuch as some of the mucus secretions were abnormally viscid, this name seemed appropriate. With the recent demonstration by di Sant'Agnese and others (1954) of the involvement of sweat glands,[4] the name mucoviscidosis no longer seems fitting as it does not encompass this additional disturbance of electrolyte excretion. No newly proposed name seems to fulfill our need. The name originally proposed by Glanzmann,[5] "dysporia enterobronchopancreatica congenita familiaris," although descriptive, is unwieldy. Therefore, in view of the lack of a suitable and generally acceptable name for this disease, it seems best, for the present, to refer to it by the name originally used by Andersen, cystic fibrosis of the pancreas.*

Plan and Methods of Study

Selection of Patients

The patients included in this report have been studied at the Children's Medical Center, and for the most part in the Chronic Nutrition Clinic, from July, 1947, to March, 1956. The majority of patients were referred to us because of clinical manifestations suggesting cystic fibrosis. The chief symptoms in all but two patients were pulmonary. Three patients are younger siblings of known patients with cystic fibrosis. The patients varied in age from 2 months to 16 years when first seen. Four patients died. The remaining 14 patients are still under observation and treatment.

Methods of Study

Clinical.—The patients were under the care of a small group of physicians during the entire period of study. Continuous medical care and advice was available at all times. Periodic clinic visits were made at intervals which varied with the condition of the patient, from one or two weeks to long intervals of four or five months. During each visit a detailed medical record was made in addition to the physical examination. The treatment plan for these patients has been presented elsewhere.[6] Laboratory studies, including x-rays of the chest, duodenal intubations, and "sweat" tests, were performed when indicated and usually on an outpatient basis.

Laboratory.—The laboratory tests, including methods, range of values, and interpretation, are given in Table 1.

1. Duodenal Fluid: The duodenal fluid was collected in the morning after a nine-hour fast. The Levin tube was passed through the nares into the duodenum with the patient under the fluoroscopic screen. The collection of the fluid was our responsibility, thereby assuring proper specimens for study, and at the same time minimizing the trauma of the procedure to the patient. Fractional specimens were collected in test tubes kept in an ice bath. They were analyzed immediately for the viscosity,[7] pH, and for proteolytic activity within one or two hours after collection. The method is usually referred to as one for "tryptic" activity and is based on gelatin liquefaction, as described by Andersen and Early.[8] The specimens were then placed in the deep freeze and stored until a convenient time, when they were examined for proteolytic activity, using gelatin as a substrate[9] and by another method with a casein substrate,[10] for amylase,[10] lipase,[11] and in many instances for carboxypeptidase[7] and chymotrypsin activity.[12] In five patients pancreatic function was studied by analyzing successive duodenal fluid specimens following intraduodenal olive-oil instillation which served as a pancreatic stimulus. Viscosity measurements were made with the Ostwald viscosimeter beginning in November, 1947, and these have become part of our routine assay. Prior to 1951, the gelatin liquefaction method described by Andersen and Early was the principal and often the only enzyme assay performed, with the modification of using larger volumes of duodenal fluid in order to obtain an end-point in specimens with relatively little activity. Since 1951, a variety of known methods have been used for each of the digestive enzymes in addition to newly introduced techniques. Our interest in methodology was aimed at selecting reliable procedures which we could perform readily in our laboratory. During the past year our routine enzyme assay has consisted of the following procedures listed under D in Table 1; 1a, 1b, 1c, 3, 4, and 5. From January, 1947, to March, 1956, we performed approximately 2500 duodenal intubations. In the last 1200 patients the duodenal fluid specimens were analyzed by

* Reference 6; the majority vote of those attending the Ross (M&R.) Conference on this disease held in Iowa City in Sept., 1955, voted in favor of continuing the name cystic fibrosis of the pancreas as first choice with fibrocystic disease of the pancreas as an alternate name.

multiple enzyme determinations. We are excluding our early studies with Farber and Maddock† which covered a two-year period (1940-1942) and included more than 150 complete assays by techniques other than those mentioned in Table 1. In retrospect we suspect that only one patient with partial pancreatic insufficiency was encountered in this early study.

† References 13-15.

TABLE 1.—*Laboratory Studies*

Duodenal Fluid Measurements
A. Volume—ml. per hour
B. pH—pH paper
C. Viscosity—gross observation when poured or pipetted is often helpful. The measurement is made with an Ostwald viscosimeter of 4 ml. capacity, having a flow time of 33 seconds with distilled water at 30 C. Our measurements, for the most part, were made at 4 C. Normal duodenal fluid at 4 C has a flow time of 50 to 120 seconds. Arbitrary upper limit of normal is 180 seconds. The viscosity from 90% of patients with cystic fibrosis is over 180 seconds.
D. Enzyme measurements:
1. Proteolytic activity (5 methods)
a. Gelatin (Andersen & Early [6])

Test Tube No.	1	2	3	4	5	6	7	8	9	10	11
Dilution of duodenal fluid (D.F.)	Undil.			1/10					1/100		
Volume of dil. of D.F. used in each tube	1.0	0.5	0.2	1.0	0.8	0.6	0.4	0.2	1.0	0.5	0.2
Actual amount of D.F. in each test tube	1.0	0.5	0.2	0.1	0.08	0.06	0.04	0.02	0.01	0.005	0.002
Normal	+	+	+	+	+	+	+	+	+	+	+
									0	0	0
Partial pancreatic insufficiency (P.I.)	+	+	+	+	+	+	+	+	0	0	0
				0	0	0	0	0			
Complete P.I.	0	0	0	0	0	0	0	0	0	0	0

+=digestion of gelatin
0=no digestion

b. 8.0% Gelatin substrate—viscosity change (Leubner & Shwachman [9])

Normal duodenal fluid	over 5
Partial P. I.	0.3 to 4.8 units
Complete P. I.	0 to 1.2 units

c. Casein substrate (Free & Myers [10])

	Mg. tyrosine Released
Normal duodenal fluid	20 to 80
Partial pancreatic insufficiency	1.5 to 25
Complete pancreatic insufficiency	0.0 to 7

d. Casein turbidity [7]

	Units
Normal duodenal fluid	over 30

e. Casein titration [7]

	Units
Normal duodenal fluid	over 10

2. Carboxypeptidase (Ravin & Seligman [7])

	μg. β Napthol Released
Normal duodenal fluid	over 0.4
Partial pancreatic insufficiency	0 to 1.0
Complete pancreatic insufficiency	below 0.4

3. Chymotrypsin (Ravin, Bernstein, & Seligman [11])

	μg. β Napthol Released
Normal duodenal fluid	over 5 to 65
Partial pancreatic insufficiency	5 to 65
Complete pancreatic insufficiency	0 to 5

4. Amylase (Free & Myers [10])

	Mg. Glucose Released
Normal duodenal fluid	4 to 20
Normal duodenal fluid under 6 mo.	0

5. Lipase (Nothman et al. [11])

	Ml. 0.1 N NaOH
Normal duodenal fluid	3 to 10

TABLE 1.—*Laboratory Studies*—Continued

Vitamin A Absorption*		
Oral dose 0.1 ml. oleum percomorphum/lb.	Fasting	4-to-5-Hour Level
Normal	10-25 units	Four- to tenfold rise over fasting 75 to 150 units
Defective Absorption	usually 1 to 10	less than a fourfold rise over fasting usually under 40 units
Gelatin Absorption*†		
1.75 gm. gelatin/kg.	Fasting Glycine Nitrogen	Postprandial Rise at 2½ Hr.
Normal	0.3	over threefold
Defective digestion	0.3	less than threefold rise
Sweat Electrolytes†		
	No. of Patients	Mean Values Na mEq/L. Cl mEq/L.
Normal	128	22.0 29.9
Cystic fibrosis with complete pancreatic insufficiency	66	112.4 116.9

* References 16 and 17.
† H. Shwachman, M. Stern, E. Higgins, and R. R. Dooley, unpublished data.

2. Sweat Electrolytes: The method of collecting sweat and the diagnostic significance of the sweat sodium and chloride concentration has been described briefly[7] and will be the subject of a future report. The sweat test was performed in 14 of the 18 patients. The test was not done on the four remaining patients because they had either died or were not available to us after July, 1954, which was the time we first developed a practical and reliable method of collecting and analyzing thermal sweat.

3. Absorption Studies:

Vitamin A. In the study of patients with complete pancreatic insufficiency the vitamin A-absorption test has been considered of diagnostic aid.[16] When vitamin A is administered in the form of oleum percomorphum in a dosage of 0.1 ml/lb., the typical response is a failure of the blood level of vitamin A to rise in the postprandial specimens. We have followed the suggestion of Pratt[17] in comparing the four- or five-hour postprandial specimen with the fasting one. This test was made in 11 patients.

Gelatin absorption test. This test is performed by feeding 1.74 gm. of gelatin per kilogram of body weight ‡ and measuring the glycine nitrogen in plasma in the fasting and the 2½ hour postprandial specimen.[18] A healthy person shows a postprandial rise of at least 2.5 times the fasting value. In complete pancreatic insufficiency the rise is insignificant. We have performed this test on seven patients.

Other Studies.—Stool trypsin examinations using a gelatin film[19] were made in patients under 4 years of age. A number of routine laboratory tests were performed, such as urine examination, blood counts, tuberculin testing, and determination of the nasopharyngeal flora. Liver function tests, electrocardiograms, and other special procedures were done when indicated. Roentgenograms of the chest were made in each patient and repeated at frequent intervals. In some cases the roentgenogram suggested the diagnosis from the appearance of the chest film. Bronchograms were made in four patients.

‡ Maximum dose used is 40 gm. of gelatin.

Results

The patients are presented in two groups for convenience of discussion. Group I includes the four fatal cases. Group II includes 13 patients who are still under observation and treatment. This group is subdivided; Group II-A, which includes those patients in whom progression to complete or nearly complete pancreatic insufficiency has taken place, and Group II-B, which includes those patients in whom partial deficiency and dissociation of enzyme activity is still present. An additional patient is included, a patient with meconium ileus who had incomplete pancreatic insufficiency.

GROUP I.—The pertinent data on these four patients are given in Tables 2A, 2B, and 2C. The cases are arranged in order of date of death. The diagnosis of cystic fibrosis was not made in the first patient during life because the duodenal fluid showed normal trypsin. The duodenal fluid, however, was scanty in amount; 5 ml. was obtained in two hours. The viscosity of the fluid was markedly elevated to 7 minutes 28 seconds as compared with a normal of 1 to 2 minutes. The diagnostic significance of the vis-

TABLE 2A.—*Fatal Cases of Cystic Fibrosis with Partial Pancreatic Insufficiency (Historical Data)*

No. of Patient	Birth Date, Sex	Date and Age at Death	Age at Onset of Illness	Age when first seen	Family History
1	8/29/47 M	10/5/48 13 mo.	5 wk.	6 wk.	First sibling, still-birth; younger sibling is normal
2	9/26/46 F	12/20/49 3 3/12 yr.	11 mo.	2 yr.	1 younger sibling apparently well
3	10/7/48 F	1/29/50 15 ½ mo.	2 mo.	4 ½ mo.	3 siblings died of cystic fibrosis
4	5/7/42 M	2/12/55 12 8/12 yr.	2 yr.	4 8/12 yr.	1 sibling normal; 1 sibling died at 3 days with intestinal obstruction; no postmortem

cosity change in spite of the normal trypsin was not fully appreciated at that time, November, 1947. A repeat duodenal intubation was not suggested, since our experience prior to this patient did not include observations on the progressive loss of pancreatic tryptic activity. When this patient was presented at a clinical pathological conference the main problem was to explain how a patient with typical pathological features of cystic fibrosis could have proteolytic activity in the duodenal fluid specimen during life. In this patient the duodenal fluid was examined when the patient was 3 months old and he succumbed 10 months later. Figures 1A and 1B show photographs of the microscopic appearance of the pancreas and the lung.

A second patient seen one year later with a more dramatic pulmonary change had two duodenal intubations, the first at 2½ years and the second at 3 years of age. On both occasions the duodenal fluid showed normal tryptic activity as well as a marked increase in viscosity. In spite of the normal trypsin the diagnosis of cystic fibrosis was entertained during life because of the pulmonary picture, the increase in viscosity of the duodenal fluid, and our previous failure to diagnose Case 1, coupled with a conviction con-

TABLE 2B.—*Fatal Cases of Cystic Fibrosis with Partial Pancreatic Insufficiency (Symptoms)*

No. of Patient	Gastrointestinal Symptoms			Respiratory Symptoms
	Appetite	Bowel Movements	Nutrition	
1	Poor; all food well tolerated	Normal	Adequate until respiratory illness severe	Hacking cough at 5 wk.; hospitalized at 6 wk. with severe respiratory distress and emphysema for 108 days; Recurrent cough until death
2	Normal; all food well tolerated	Constipated first year	Good until respiratory disease severe at 18 mo.	Well until 11 mo.; chronic wheeze and severe cough at 12 mo.; progressive illness with marked emphysema and cyanosis
3	Fair-poor; poor fat tolerance	Normal until 7 mo.; then frequent and foul	Adequate till 7 mo.; poor later	Dry cough at 2 mo.; respiratory distress with emphysema at 4 mo.; progressive pulmonary symptoms until death
4	Poor; all food well tolerated	Normal	Good till 7 yr.; then poor	Mild persistent cough onset at 2 yr.; at 4 ½ yr. bronchograms showed bronchiectasis of L.L.L.; subsequent progressive pulmonary failure; spontaneous pneumothorax at 10 4/12 and 11 9/12 yr.

TABLE 2C.—*Fatal Cases of Cystic Fibrosis with Partial Pancreatic Insufficiency (Laboratory Data)*

No. of Patient	Duodenal Fluid Age	Viscosity	End-Point of Gelatin Liquefaction Activity Present In	Other Tests	Pancreas at Postmortem	Lungs at Postmortem
1	3 mo.	7'28"	0.01 ml.		Gross—normal; microscopic—moderate degree acinar dilation; inspissation of secretions; relative increase of fibrous tissue	Weight 2 times normal; patchy atelectasis with emphysema; bronchiectasis; microscopic—emphysema, bronchiectasis, and diffuse bronchopneumonia
2	2 yr. 3 3/12	6'50" 20'	0.01 ml. 0.04 ml.	Stool trypsin 4+ in 1/5 and 1/10 dilution on 8 occasions	Gross—smaller than normal; firm and nodular; microscopic—increase in fibrous tissue; inspissation; dilatation of acini	Weight 2 times normal; emphysema and firm nodules throughout; bronchi filled with purulent exudate; microscopic—emphysema, bronchiectasis, and bronchopneumonia
3	4 mo. 7 mo.	2'30" 6'30"	0.06 ml. 0.5 ml.		Gross—smaller than normal; microscopic—increased fibrous tissue; numerous acini show inspissation and obstruction while a small number appear normal	Weight increased; emphysematous with scattered areas of fibrosis, and bronchiectasis; bronchi filled with purulent exudate; microscopic—emphysema, bronchiectasis, and necrotizing bronchopneumonia
4	4 8/12 9 yr.* 12 yr.*	 2' 2'	0.002 ml. 0.04 ml. 0.04 ml.	Vitamin A Absorption at 10 yr.; fast.—11.2; 5 ½ hr.—18.8; gelatin digestion test: fast.—0.25; 2 hr.—0.65; sweat electrolytes at 12 yr.—Na-145 mEq/L., Cl-175 mEq/L.	Gross—small firm; dilated pancreatic duct; microscopic—irregular areas of fibrosis; dilatation of acini, inspissation of secretions; minimal chronic inflammatory infiltrate; some acini appear normal	Weight 2 times normal; emphysematous; hilar nodes enlarged; trachea and bronchi filled with purulent exudate; patchy atelectasis; bronchiectasis; many areas of lobular pneumonia

* Low protease by other methods and low amylase, normal lipase.

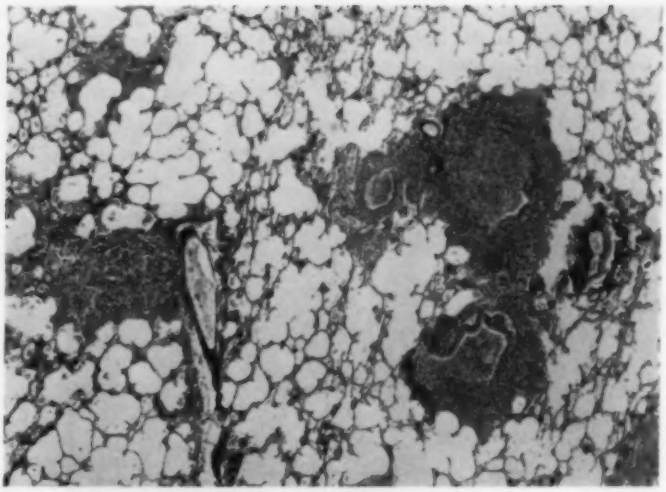

Fig. 1A (Patient 1).—Lung, × 100. This photo shows emphysema, bronchopneumonia with bronchial plugging, and bronchiectasis.

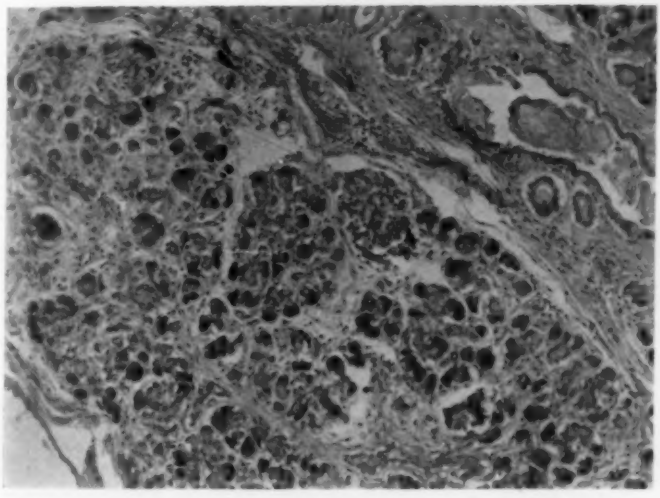

Fig. 1B (Patient 1).—Pancreas, × 150. Note the inspissated secretions in some acini and ducts, the large number of intact acini and fibrosis.

cerning this entity which was supported by existing pathological evidence. The patient succumbed at 3 1/12 years. The pancreas showed the typical features of the disease. Figures 2A, 2B, and 2C show the photographs of the roentgenogram of the chest taken one month before death and the microscopic appearance of the pancreas and lung.

The third patient presented a clinical picture more suggestive of cystic fibrosis because of the appearance of large foul stools at 7 months of age. She succumbed at 15½ months. The duodenal fluid, when first examined at 4½ months, showed tryptic activity in 0.06 ml., whereas at 7 months considerable loss had taken place so that 0.5 ml. was necessary to obtain the same end-point. The diagnosis suspected at four and one-half months was established at seven months. The family history was significant, since two siblings had already died of cystic fibrosis. Figure 3 shows the microscopic appearance of the pancreas.

The fourth patient was first seen in January, 1947, at the age of 4 8/12 years and approximately 2 years after the onset of a

chronic pulmonary infection. Cystic fibrosis was ruled out at the age of 4 8/12 because the duodenal fluid had normal tryptic activity. A photo of the chest film taken in October, 1947, is shown in Figure 4A. He was followed regularly in the "chest" clinic until June, 1952.§ At that time he was seen by one of us and the diagnosis of cystic fibrosis was again questioned. The loss of a sibling with intestinal obstruction at 3 days

§ Drs. Albert Frank and Robert Smith referred this patient to us for study and follow-up care.

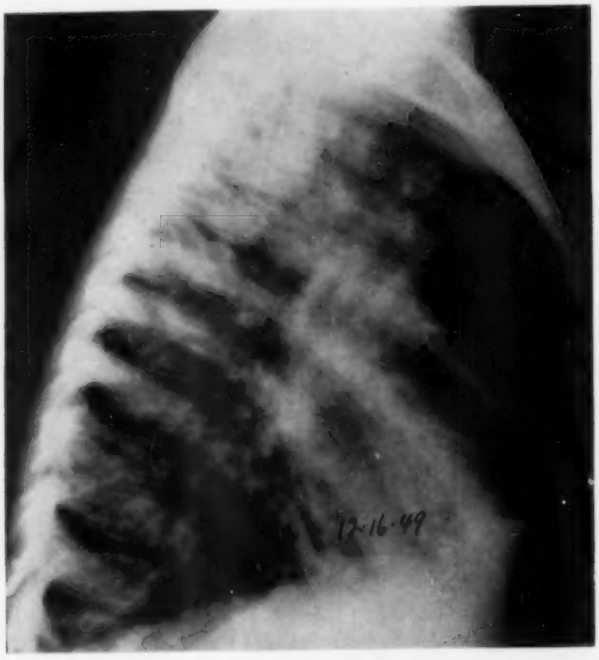

Fig. 2A (Patient 2).—Roentgenogram of chest, lateral view, on Dec. 16, 1949.

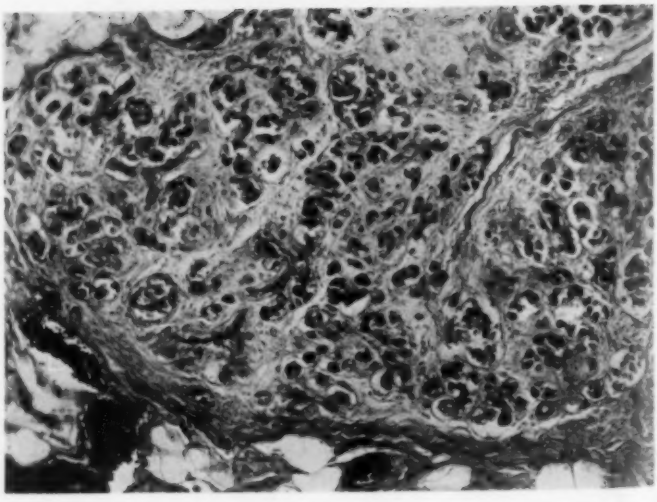

Fig. 2B (Patient 2).—Lung, × 100. Emphysema, dilatation, and plugging of bronchioles and early organizing pneumonia in a peribronchial hilar pattern.

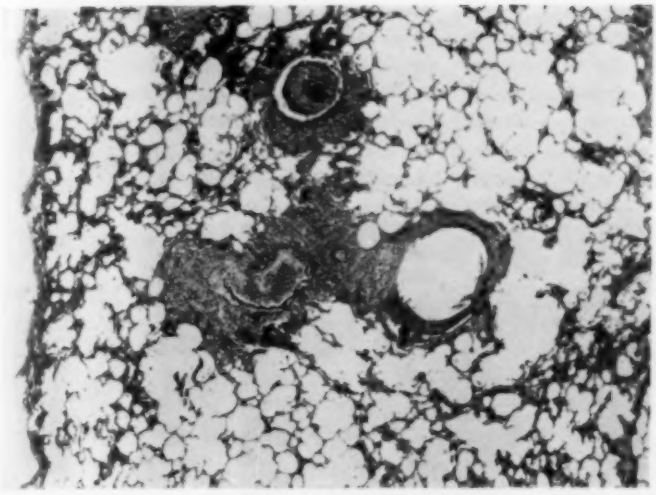

Fig. 2C (Patient 2).—Pancreas, ×150. This area shows marked atrophy and fibrosis with occasional inspissated plugs. There are a number of well-preserved acini.

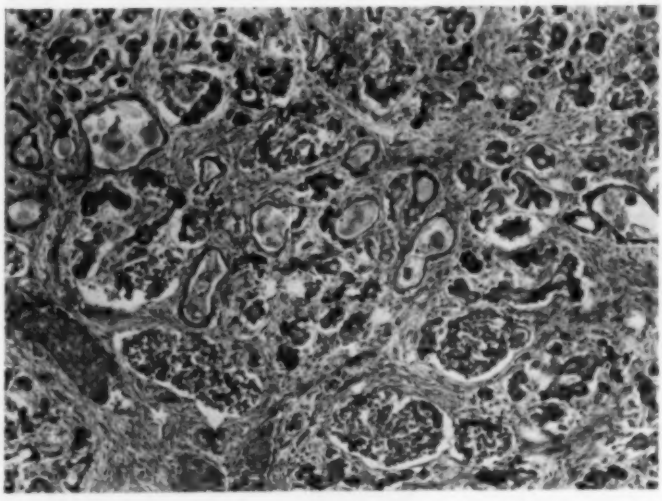

Fig. 3 (Patient 3).—This section shows inspissated secretion and dilatation of lobular ducts and moderate fibrosis with preservation of acinar tissue.

of age, suggesting meconium ileus, was taken into consideration. The duodenal fluid was reexamined, and this showed a diminished amylase activity, a normal lipase, and a slight reduction in proteolytic activity. Gelatin and vitamin A absorption studies were carried out at this time. His ability to digest proteins, as judged by the gelatin test, was unimpaired. The vitamin A absorption was impaired, a finding which did not correlate with clinical evidence of steatorrhea or ability to tolerate fats. The chronic pulmonary process was considered the chief manifestation of cystic fibrosis. He was treated with continuous broad-spectrum antibiotics and inhalation antibiotic therapy. A third duodenal intubation was done in May, 1954, and again a low amylase, a normal lipase, and some reduction in proteolytic activity were detected. The viscosity of the duodenal fluid was not abnormal in this or in the previous examination. The diagnosis of cystic fibrosis was confirmed in August, 1954, when the concentration of sodium

and chloride in the sweat was found greatly elevated. Symptoms of pancreatic insufficiency were watched for but did not occur at any time. The patient succumbed in February, 1955, as a result of chronic pulmonary infection. The postmortem examination showed changes in his pancreas which are consistent with cystic fibrosis (Fig. 4B). Figure 4B shows the microscopic appearance of the pancreas.

The common finding in these four patients is the early onset of pulmonary symptoms characterized by diffuse respiratory obstruction and emphysema. Bronchitis,

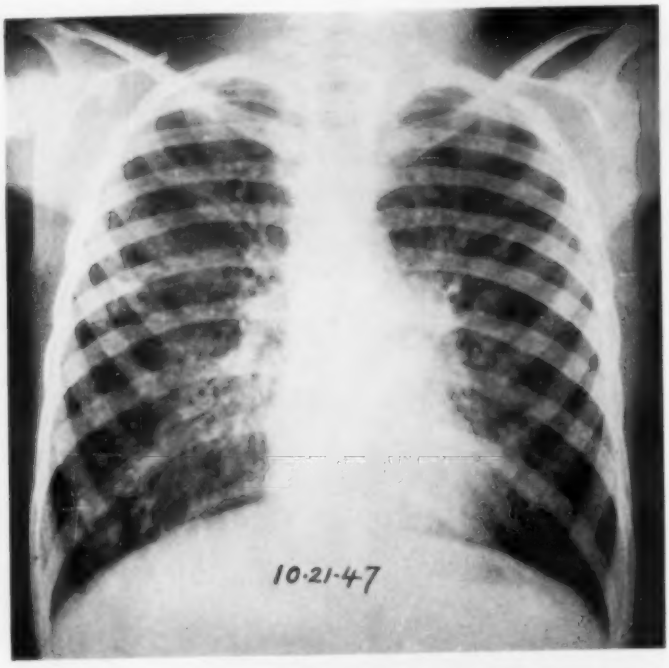

Fig. 4A (Patient 4).—Roentgenogram of chest on Oct. 21, 1947, at 5 5/12 years.

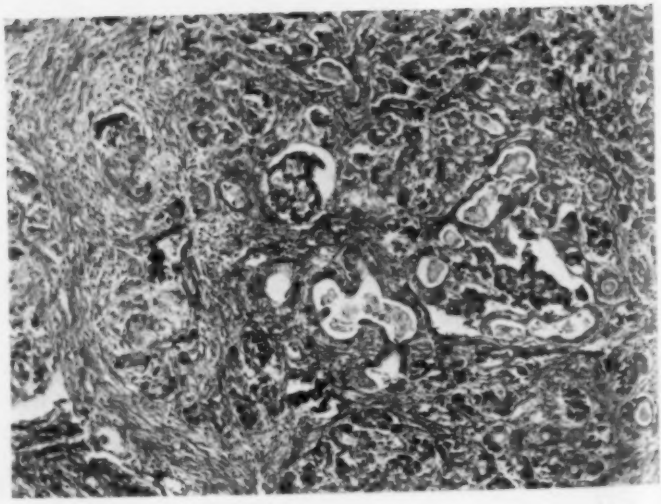

Fig. 4B (Patient 4).—Pancreas, × 150. There is marked fibrosis with some inspissated secretion in a number of widely dilated ducts. Many acini appear intact. In all sections of the pancreas the islet cells are prominent.

bronchopneumonia, and bronchiectasis followed. Death was due to the extensive pulmonary infection and insufficiency. These patients had the usual progression of pulmonary symptoms as seen in those patients in whom the diagnosis of cystic fibrosis could be readily established when the additional clinical and laboratory features of pancreatic insufficiency were present. Digestive symptoms indicative of pancreatic insufficiency were absent in three patients and present in one patient. This infant had an excellent appetite and after 7 months of age began to pass large, frequent, and foul stools. It should be pointed out that the earliest roentgenograms of the chest in each case were considered compatible with cystic fibrosis. In three patients the duodenal fluid showed normal trypsin and in one case slightly reduced activity by the gelatin liquefaction method. In three patients the duodenal fluid viscosity was abnormally increased and served as one of the laboratory features which led to the clinical diagnosis. The strong family history in one patient was very significant in pointing toward the diagnosis at a time when the pulmonary symptoms were the only ones present. The sweat test performed in one patient added further support to the diagnosis of cystic fibrosis with partial pancreatic insufficiency.

GROUP II-A.—This group includes six persons. The patients are listed in order of age in Tables 3A, 3B, and 3C, which summarize the chief features. In each case the diagnosis of cystic fibrosis was suspected and therapy begun prior to the development of complete pancreatic insufficiency. In each case the duodenal fluid when initially obtained possessed unequivocal proteolytic activity. Decreasing activity was noted on subsequent examinations with complete loss of proteolytic activity in three cases. The viscosity of the duodenal fluid was abnormally elevated in five of the six patients. The family history was positive in four patients; in two families the diagnosis in the siblings was confirmed by postmortem examination.

Patient 6 was first seen at 3 months of age with a history of persistent wheezing and severe cough. There was a history of having lost a sibling with cystic fibrosis confirmed by a postmortem examination. At 10 months of age the first duodenal intubation was done. The only test performed was that for trypsin. Because activity was present in 0.4 ml. of a 1/10 dilution of duodenal fluid, the diagnosis of cystic fibrosis was excluded. For a period of approximately 1 year beginning at 4 months of age the patient's mother noted slightly foul movements. Subsequently the movements appeared normal. The patient was followed because of his mild pulmonary complaints and our interest in him. The duodenal in-

TABLE 3A.—*Cystic Fibrosis with Progression of Pancreatic Insufficiency*

No. of Patient	Birth Date Sex	Age at Onset of Illness	Age When First Seen	Family History
5	7/ 6/45 M	2-6/12	5 10/12	Oldest sibling has cystic fibrosis; youngest sibling well
6	1/12/46 M	3 mo.	3 mo.	Older sibling died with cystic fibrosis; younger sibling is well
7	9/11/49 M	Neonate 1-2 wk.	2 mo.	2 younger siblings are well
8	9/20/49 F	3 wk.	4 mo.	No siblings
9	2/16/50 M	2 yr.	7 mo.	Older sibling died with cystic fibrosis
10	12/30/51 M	No symptoms	7 mo.	1 healthy sibling; 2 siblings have cystic fibrosis

TABLE 3B

No. of Patient	Gastrointestinal Symptoms			Respiratory Symptoms
	Appetite	Bowel Movements	Nutrition	
5	Fair to poor; never excessive	Normal 5 yr.; bulky, foul since	Weight good till 8 yr.; poor since	Pneumonia at 2½ yr.; chronic hacking cough since then; slow but progressive involvement since with bronchiectasis; now far advanced
6	Good; not voracious	Slightly foul at 4 to 5 mo., for 1 yr.; then normal	Excellent	Wheeze—3 mo.; mild intermittent cough with infections since; intermittent antibiotics for years
7	Very good	Foul, bulky, 2 to 5 per day for first 3 months; then gradual improvement	Poor from beginning	Cough 7 wk.; pneumonia 2 mo.; intermittent cough since; respiratory symptoms still mild; on antibiotics since 9 wk. of age
8	Very good	Loose, foul and frequent until 4-5 mo.; marked improvement with treatment	Poor after 3 wk. to 4 mo.; at 3 mo. weight 8 lb. 8 oz.; at 5 yr. in 40 percentile for weight	Cough at 3 mo.; intermittent since with colds, never severe; constant antibiotics
9	Normal	1-2 per day; formed, normal	Excellent	Severe cough with U.R.I. lasting weeks since 2 yr.; intermittent antibiotics
10	Normal	Normal	Excellent	Mild cough with U.R.I.; intermittent antibiotics

tubation was repeated in January, 1951, when he was 5 years of age. No change in tryptic activity had taken place. A third intubation at 6 years of age revealed no proteolytic activity in the duodenal aspirate by the previously used method, as well as by a number of other methods. The duodenal fluid at this time had no lipase or amylase activity. Pancreatic replacement therapy was begun after the demonstration of pancreatic insufficiency. We should like to call attention to the significant rise in the vitamin A-absorption test when it was done at 2½ years of age. The gelatin ab-

TABLE 3C

No. of Patient	Duodenal Intubation							
	Age	Viscosity	Amylase	Lipase	End-Point of Gelatin liquefaction Activity Present in	Casein Turbidity	Casein Titration	Carboxypeptidase
5	6 yr.	2'36"			0.04 ml.			
	7 1/12	10'	6.4	2.3	0.2 ml.	5	0	0.12
6	10 mo.	Not done			0.04 ml.			
	5 yr.	2'19"			0.04 ml.			
	6 yr.	2'25"	0	0	0.12 ml.			0.05
7	9 wk.	3'			0.02 ml.			
	4 mo.	>15'			0.04 ml.			
	8 mo.	>15'			0.04 ml.			
	1 yr.	3'48"			0.04 ml.			
	3 yr.	>10'	10.8	12.0	0.06 ml.	5	2	0
	3 7/12	>10'	0	0.3	0.5 no digestion	0	0	0
8	3½ mo.	5'10"			0.04 ml.			
	5 mo.	15'			0.6 no digestion			
	1 yr.	15'			0.6 no digestion			
	2 7/12	15'	0.2	0.1	1.0 no digestion	0	0	0.04
9	1 yr.	20'			0.01 ml.			
	2 yr.	12'	0.3	0.1	0.12 ml.	7	0	0.04
10	7 mo.	6'59"			0.04 ml.			
	11 mo.	9'22"	0.5	9.8	0.08 ml.	14	2	0.20
	3 5/12	15'43"	0.5	2.6	1.0 no digestion			

TABLE 3C—Continued

Sweat Electrolytes			Vitamin A			Glycine		
Age	Na (mEq/L)	Cl (mEq/L)	Age	Fasting	3½ Hr.	Age	Fasting	2½ Hr.
9 2/12	106		6 yr.	14.7	19.04			
8 10/12	96	120	2 2/12	11.6	51.8	3 5/12	0.62	2.05
5 2/12	120	133	2/12	9.5	30.9	2/12	0.22	0.8
			3 8/12	11.4	12.6	5/12	0.3	1.10
6 11/12	88	102	3½ mo.	5.3	8.2	3½ mo.	0.3	1.94
			14 mo	30.5	80.9			
			2 yr.	6.2	58.9	2 yr.	0.35	
2 8/12	82	85						

sorption test was also normal when performed at 3 5/12 years of age at a time when pancreatic function was presumably unimpaired.

Patients 7 and 8 were alike in the early appearance of pulmonary symptoms accompanied by mild gastrointestinal complaints. In the case of Patient 7 the duodenal intubation was performed six times over a period of 3½ years before complete pancreatic enzyme deficiency occurred. In the case of Patient 8 marked loss of tryptic activity was observed between 3½ and 5 months of age.

Patients 9 and 10 are of interest in that they were asymptomatic at the time of the first intubation. They were examined because an older sibling had the disease. In each case the duodenal aspirate was markedly abnormal with regard to viscosity, yet possessed normal proteolytic activity. When the duodenal intubation was repeated at a later date, moderate reduction of proteolytic activity was detected with a persistence in the altered viscosity. The lipase and amylase values were also markedly depressed. The original duodenal fluid from both children was cultured on routine bacteriologic media with no resultant growth. Both patients are still asymptomatic, although Patient 9 may have a persistent and prolonged cough with respiratory infections.

During our investigation three patients in this group were subjected to a pancreatic stimulus and the nature of the response studied. The absence of enzymes in a fasting specimen of duodenal fluid does not necessarily mean that the pancreas is exhausted and will not respond when it is stimulated either by food substances or by intravenous secretin. We use 10 to 15 ml. of intraduodenal olive oil as the stimulus and compare the enzyme activity of the fasting duodenal fluid specimen with a number of specimens obtained after the stimulus. Table 4A shows the results obtained. In the case of Patient 6 the pancreas failed to respond, thus indicating complete loss of pancreatic enzyme production. Patient 9, although possessing low fasting enzyme values, shows some increase in proteolytic, amylase, and lipase activity in specimen number four taken 40 minutes after the instillation of olive oil. In the case of Patient 10 no significant change was observed after the pancreatic stimulation. In all three cases the response is unlike that usually ob-

TABLE 4A.—*Enzyme Response to Pancreatic Stimulation by Intraduodenal Olive Oil in Patients with Pancreatic Insufficiency*

Patient	Age	Specimen of * Duodenal Fluid	Proteolytic Activity				Amylase	Lipase	
			Casein Titra.	Casein Turbid.	Gelatin End-Point	Carboxy-peptidase	Sugar	Olive Oil	Tributyn
6	6 yr.	Fasting	2	0	0.12	0.05	0	0.21	0.1
		#4—15 min.	0	0		0.06	0	0	0.3
		#5—30 min.	0	0		0.04	0	0.05	0.4
		#6—50 min.	0	0		0.06	0	0	0
9	2 yr.	Fasting	0	7	0.12	0.04	0.3	0.1	0.1
		#4—40 min.	4	23		0.19	2.8	3.2	7.7
		#5—60 min.	2	4		0.04	0.3	0.1	0.4
		#6—80 min.	12	5		0.01	0.5	0	0
10	11 mo.	Fasting	2	14	0.08	0.26	0.5	9.8	0.6
		#5—60 min.	0	0		0.25	0.3	9.0	1.1
		#6—80 min.	0	1		0.19	0.5	8.3	0.9
		#7—100 min.	3	8		0.11	0.2	9.8	1.3

* Four separate specimens were analyzed in each case. The fasting one and three following the stimulation with olive oil. Approximately 10 ml. of olive oil was introduced through the Levin tube and specimens were collected at frequent timed intervals thereafter. The specimen number and time of beginning of collection is indicated.

TABLE 4B

Patient	Age	Specimen of Duodenal Fluid	Proteolytic Activity					Amylase	Lipase	
			Casein Titra.	Casein Turbid.	Casein Tyrosine	Gelatin End-Point	Carboxy-peptidase	Sugar	Olive Oil	Tributyn
11	16 2/12	Fasting	8	..	0	0.01	0	0.0	4.4	2.3
		#4—30 min.	2	..	1.8		0	0.8	3.5	0.4
		#5—45 min.	5	..	10.6		0	4.9	4.2	0.8
16	2 4/12	Fasting	15	40		0.04	0.39	15.2	3.9	9.0
		#6—45 min.	17	40			0.17	6.2	12.8	2.6
		#7—65 min.	5	7			0.10	2.1	6.4	1.9

TABLE 5A.—*Cystic Fibrosis with Partial Pancreatic Insufficiency and Dissociation of Enzyme Activity*

No. of Patient	Birth Date and Sex	Age at Onset of Illness	Age When First Seen	Family History
11	11/15/37 M	6 yr.	9 yr.	Older sister similar history and course
12	1/ 5/43 M	3 mo.	3 4/12 yr.	No siblings
13	11/ 6/44 M	3 wk.	5 mo.	1 younger sibling
14	9/ 3/45 F	18 mo.	6 yr.	Only child
15	2/20/48 M	6 wk.	6 mo.	4 siblings are healthy
16	10/15/49 M	6 mo.	3 4/12	2 oldest siblings healthy; 1 had meconium ileus and 1 has cystic fibrosis
17	9/19/52 M	2 wk.	5 wk.	2 siblings have been suspected of having cystic fibrosis; tests so far negative for cystic fibrosis

served in healthy children where a two- to fivefold increase of enzyme activity occurs in approximately 40-60 minutes after the olive-oil Stimulus.

When the sweat test became available five patients were recalled for this test and in each case the characteristic abnormality noted in cystic fibrosis was detected. Two patients lived at a distance and for this reason did not have the sweat test.

GROUP II-B.—In each of the seven patients placed in this group and listed in Tables 5A, 5B, and 5C, the duodenal fluid shows a dissociation of, or lack of correla-

TABLE 5B

No. of Patient	Gastrointestinal Symptoms			Respiratory Symptoms
	Appetite	Bowel Movements	Nutrition	
11	Normal	1 per day; normal until 11 yr., since then bulky	Normal	Mild chronic cough for 7 yr.; repeated episodes of pneumonia; asymptomatic on antibiotic therapy
12	Normal	Normal	Good up to 3 yr. from 4 yr. in 10 percentile for weight	Recurrent pneumonia; 1st attack at 3 mo. & 1 each winter for 3 yr.; bronchoscopy at 4 yr. revealed bronchiectasis involving all lobes; progressive incapacity past 2 yr.
13	Never excessive	Normal	Always husky; well nourished	Wheeze during first month; pneumonia at 4 mo.; hospitalized for 3 mo.; improved on constant antibiotics
14	Fair	1 to 2 per day; normal	Excellent till 6 yr.	Intermittent cough at 18 mo.; chronic progressive cough from 3 yr. to present
15	Fair	1 to 2 large	Good till 1 year, then fair	Chronic progressive cough since 6 wk.; now emphysema, far advanced; bronchiectasis
16	Fair—poor	Occasional diarrhea; normal	Good till 2 yr.	Repeated pneumonia from 6 to 13 mo.; severe cough, progressive emphysema; improvement on antibiotic therapy
17	Marked increase from birth	2-3 per day; light in odor	Poor wt. gain	Severe cough at 2 wk.; mild intermittent since; no emphysema or clubbing

TABLE 5C

No. of Patient	Sweat Electrolytes			Duodenal Intubation				End-Point of Gelatin Liquefaction Activity Present in	Gelatin Viscosity
	Age	Na (mEq/L.)	Cl (mEq/L.)	Age	Viscosity	Amylase	Lipase		
11	16 10/12	110	121	13 yr. 15 3/12 16 2/12	1'50" >15' >15'	1.5 0	3.9 4.4	0.04 ml. 0.02 ml. 0.01 ml.	
12	12 11/12	80	96	3 4/12 12 11/12	3'		1.4	0.02 ml. 0.2 ml.	0.0
13	9 yr.	112	114	4 11/12 5 5 3/12 8 7/12	2'7" 2'25" 2'05" 1'35	3.2	3.8	0.04 ml. 0.04 ml. 0.04 ml. 0.04 ml.	1.5
14	9 2/12	145	131	6 3/12 7 1/12 7 7/12	6 6'10" 5 25"	3.4 0	16.6 9.4 3.0	0.002 ml. 0.01 ml. 0.02 ml.	
15	6 7/12	117	112	6/12 9/12 1 yr. 3 6/12 6 4/12	4'1" >10' >10' 1'16" >10'	0.8	0 4.4	0.2 ml. 1.0 ml. no digestion 1.0 ml. no digestion 0.01 ml. 0.5 ml. no digestion	7.3
16	5 2/12	118	122	2 4/12	15'	15.2	4.0	0.04 ml.	
17	2 3/12	65	67	1/12 2 9/12	3' 1'55"	0 3.2	0.2 2.0	0.02 ml. 0.01 ml.	15.5

tion of the activity of the various pancreatic enzymes. For example, in the case of Patient 14 the amylase values are low to zero with a gradual decline of lipase activity at a time of relatively good proteolytic activity.

The diagnosis of cystic fibrosis in these patients could not be made on the basis of tryptic activity of the duodenal fluid when they were first studied. In six patients the viscosity of the duodenal fluid was increased. We have not observed this group sufficiently long to be able to report complete loss of enzyme activity, although individual patients have been seen for four and five years. When two patients in this group were given intraduodenal olive oil as a pancreatic stimulus, an inadequate response ensued. (Table 4B). In Patient 11 the amylase and protease activity increased in the 45-minute specimen, whereas in Patient 16 a fall in most values occurred with the exception of the rise in lipase.

The vitamin A-absorption test was done in four patients, and in three there was an abnormal response with very little rise in the vitamin A level in the postprandial specimen. In three patients the gelatin absorption test was performed; in one patient the response was normal, in one borderline, and in the third patient the response was abnormal.

The clinical features of these patients differs in no way from those in Group II-A. The pulmonary symptoms appeared in infancy or early childhood, to be followed by mild gastrointestinal symptoms in only three patients at a later age. The majority of patients enjoyed a normal appetite in contrast to the infants with complete pancreatic insufficiency who have voracious appetites. However, appetite was poor when the pulmonary infection was severe. The family history is significant in four patients because another member of the family has the disease. In six patients who were recalled in order to have the sweat test done, an abnormally high sweat sodium and chloride concentration was found in each case.

In the presentation of data on partial pancreatic insufficiency in cystic fibrosis we should like to mention one additional patient, an infant with meconium ileus who required surgical relief of her obstruction at 1 day of age. This child, unlike most in-

TABLE 5C—Continued

Casein Turbidity	Casein Titration	Casein Tyrosine	Chymotrypsin	Carboxypeptidase	Vitamin A			Glycine		
					Age	Fasting	5½ Hr.	Age	Fasting	2½ Hr.
9	2 8	0	0	0.21 0						
		3.5	5.5		3 1/12		9.43			
1	9	11.8	0.17	0.17	2 3/12	3.97	19.3	2 3/12	0.42	1.42
43 54 21	36 9 12			0.79 0.52	6 yr.	21.0	26.5			
		27	2.6		3/12	5.3	8.2	6/12	0.3	0.8
40	15			0.39	2 8/12	10.0	17.9	2 8/12	0.31	0.30
7	2	22.4	22.8	0.02						

fants with meconium ileus, had some evidence of pancreatic exocrine function at 1 month of age. When the duodenal intubation was repeated four months later, there was further loss of activity. The essential data on this baby follows:

A girl was born April 15, 1954. Operation at 1 day. Developed right upper lobe atelectasis at 6 weeks requiring hospitalization for 2½ months. At present has moderate pulmonary involvement with emphysema and early clubbing. Her nutritional state is poor, as she is below the 10th percentile for weight. Sweat test at 4 months showed a high sodium of 108.0 mEq/liter. Repeated at 5 months and sweat sodium was 108.4 mEq/liter and chloride 139.0 mEq/liter. The duodenal intubations at one month and five months are listed:

Age	Visc.	Amylase	Lipase	Gelatin Liquefaction	Gelatin Viscosity	Casein Tyrosine	Chymotrypsin
1 mo.	1'55"	0	3.1	0.04 ml.	1.85	7.2	....
5 mo.	2'41"	0.1	1.6	Qns.	0	0	1.7

In our experience only two other infants with meconium ileus showed significant tryptic activity of the duodenal fluid at 1 month of age. A detailed clinical study of 20 surviving patients with mecominum ileus has been reported.[20]

Comment

The syndrome of partial pancreatic insufficiency as presented in this report is supported by pathological evidence in the four fatal cases. The sections of the pancreas clearly indicate varying degrees of acinar cell involvement. The long delay in the recognition of this clinical syndrome is probably explained by the tremendous reserve power of the pancreas and the relatively crude methods of ascertaining varying degrees of pancreatic dysfunction. The literature includes a number of examples in which duodenal fluid was found to possess adequate and varying amounts of enzyme activity in patients who later died and showed evidence of cystic fibrosis at postmortem examination. O'Neil[21] clearly demonstrated, in her study of 31 patients with cystic fibrosis, low enzyme values in the

duodenal fluid in a small number, suggesting to her a possible correlation between enzyme activity during life and the microscopic findings at necropsy. Zuelzer and Newton [22] in a study of 36 patients mentioned one infant who during life showed loss of tryptic activity of duodenal fluid from 20% of normal to complete absence. They pointed out the greater degree of involvement of the pancreas in patients who succumbed at a later age, indicating that some type of progressive change may take place in the pancreas with increasing age. Bodian [23] refers to one infant who died at 11 months of age from the pulmonary aspects of the disease, although shortly before death the tryptic activity of his duodenal fluid had been normal. He also stated that "clinical and pathological evidence has shown that in most cases the pancreatic lesion is sufficiently advanced in early infancy to cause absence of the pancreatic enzymes in the duodenum; in a small proportion, however, possibly no more than 5%, there is evidence to show that the lesion is incomplete for some months or years after birth." The careful work of Gibbs and co-workers [1] provides two additional patients with postmortem confirmation in whom enzyme activity was present in the duodenal fluid during life.

Confusion may arise in the interpretation of duodenal enzyme findings when one fails to observe uniform or parallel activity for amylase, lipase, and trypsin. The early studies of Andersen [6] and Farber and associates ‖ are in accord with current physiologic teaching, namely, that there is more or less parallel activity of the digestive pancreatic enzymes in the duodenal fluid. These investigators found little or no activity for amylase, lipase, and trypsin in patients with cystic fibrosis of the pancreas, whereas in

‖ References 13, 14, and 15.

TABLE 6.—*Protease Activity (Gelatin Liquefaction) and Viscosity of Duodenal Fluid in One Hundred Patients with Cystic Fibrosis*

Dilution	Undiluted					1/10								1/100			Viscosity	
																	3 Min.	
Volume, ml.	1.0	0.8	0.6	0.4	0.2	1.6	1.4	1.2	1.0	0.8	0.6	0.4	0.2	1.0	0.5	0.25	Under	Over
Normal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ or 0	0	Yes	No
																	No. of Patients	
No. of Patients 73	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	71
2	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		2
2	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
1	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0		1
6	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	2	4
2	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0		2
1	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	1	
1	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0		1
3	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0		3
2 (1)	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0		2
1	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0		1
3 (2)	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0		3
2 (1)*	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0		2
(1)†	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0		1

( ) Refers to patients who died. The postmortem examination confirmed the diagnosis of cystic fibrosis.
* Patient 2 of this report.
† Patient 1 of this report.

healthy children and in a large group of patients with miscellaneous illnesses relatively good activity was detected for each of the above enzymes. The only exception noted was in the amylase, which is absent from the duodenal fluid of healthy infants under 6 months of age. These studies justified the acceptance of a single-enzyme assay method for determining the exocrine function of the pancreas. The tryptic activity was selected for routine assay, since the methods for amylase and lipase seemed more time-consuming and less reliable and appeared to add little information.

Laboratory evidence suggesting a state of partial pancreatic insufficiency was noted in 1948,[18] when we were studying protein digestion with oral gelatin feeding. In six patients with reduced tryptic activity of the duodenal aspirate, intermediate values for protein digestion were obtained. The stool-trypsin test[19] also provided suggestive evidence for this syndrome. In any one patient we interpreted one positive stool-trypsin test in a series of negative tests as due to pancreatic trypsin rather than a bacterial gelatinase. The studies with olive-oil stimulation have shown that a presumably inactive pancreas may respond by producing small, yet significant pancreatic enzymes. This physiologic response may explain the occasional appearance of a positive stool-trypsin test in an infant with a remnant of functioning acinar tissue. Equally important is the appreciation of this response when performing metabolic balances on patients with cystic fibrosis. One may draw false conclusions when interpreting fat and nitrogen balance data if one ignores the possibility of stimulating responsive acinar tissue by the ingestion of food.

Another laboratory measurement we emphasized was the viscosity of the duodenal fluid. The significance of altered viscosity of duodenal fluid in cystic fibrosis was discussed at the American Pediatric Society by Shwachman, Patterson, and Farber in May, 1950. Table 6 is taken from this unpublished paper. In this table the protease activity (gelatin liquefaction) of duodenal fluid is compared with the viscosity in 100 patients diagnosed as having cystic fibrosis. The problem of where to draw the dividing line between normal and abnormal protease activity is apparent. The diagnosis is certain when 1.0 ml. of the duodenal fluid shows no activity, as was the case in the 73 patients listed on the top line of the table. However, when one examines the last case listed in the table, in which proteolytic activity was found in 1.0 ml. of a 1/100 dilution of the duodenal fluid, one is bound by former criteria to discard the diagnosis of cystic fibrosis. Actually, this patient is Patient 2 of Table 1. Of the 12 patients listed at the bottom of the table, 5 succumbed, and in these the postmortem examination showed evidence of cystic fibrosis. In the remaining seven cases subsequent reduction in enzyme activity occurred as was illustrated in one report[25] and as shown in this report. The abnormal viscosity noted in these 12 cases, as well as in the group as a whole, points to the usefulness of this measurement. We do not understand why the duodenal fluid in 6 of the 100 patients was found to have a normal viscosity. There appears to be no relationship between protease activity and altered viscosity. Unfortunately, the viscosity could not be measured on every sample collected because of inadequacy of the specimen. This occurred in approximately 10% of the patients with cystic fibrosis. The viscosity has been found elevated in a few patients with other conditions, such as rheumatic fever and asthma, and in a few adults with diabetes. We hope that the explanation for the chemical and physical alteration of the duodenal fluid will be found. With this may come a new technique which might have a diagnostic application as well as provide an explanation for a poorly understood metabolic defect.

The unreliability of the "tryptic" assay of duodenal aspirate in establishing the diagnosis, as illustrated in Table 6, led us to consider other methods of enzyme assay. Not only did we employ a variety of methods for determining proteolytic

activity but also a number of procedures for amylase and lipase activity. These studies make us question the concept of parallel activity of enzymes in the affected organ. In the partially affected pancreas one may get a dissociation of activity. Nor can one predict which of the enzymes will be lost first in those patients who show progressive involvement. Eventually all activity is gone, and the rate at which this process takes place may vary considerably from patient to patient. One may predict that nearly all the patients listed in Group II-B will eventually show further loss of pancreatic function. We advocate the use of replacement pancreatin therapy when symptoms of pancreatic insufficiency occur or when laboratory findings indicate more than 70% to 80% loss of enzyme production. We have not employed pancreatin in patients with little or no deficiency. We do not suspect that pancreatin administration would retard the progression of the pancreatic lesion.

The above observations suggest caution in the use of a trypsin assay of the duodenal fluid as a reflection of pancreatic function. The marked fluctuation in activity of this organ and the wide normal range of activity of some individual components must be considered in evaluating pancreatic status. A number of tests reflecting different functions of the pancreas may provide a truer index of the status of the pancreas. The so-called direct tests of pancreatic function include the following measurements of duodenal fluid: pH; volume secreted per unit time; bicarbonate secretion; viscosity; enzyme activity, including protease, amylase, lipase, and others if possible, and, finally, the response to intravenous secretin or intraduodenal olive oil. The indirect tests may contribute useful information regarding pancreatic function. These tests include fat and nitrogen balance, absorption tests for fats, including vitamin A and proteins, and, finally, the stool-trypsin test.

One can anticipate certain difficulties which may arise in the pathological confirmation of a diagnosis of cystic fibrosis where the lesion has only minimally affected the pancreas. It is quite possible that patients in Group II-B who have adequate pancreatic function may succumb as a result of some unrelated event, i. e., accident or severe pulmonary disease, and show minimal or questionable changes in the pancreas. Our colleague in the Department of Pathology, John Craig,¶ can frequently arrive at a correct diagnosis from the histological appearance of the lungs and bronchi and at times be aided by changes in other organs or in mucus-secreting tissue. di Sant'Agnese [2] reported one patient in whom a biopsy of the pancreas was obtained and found to be normal, and who later was diagnosed as having cystic fibrosis.

In one case reported by Lowe and May [20] as selective pancreatic deficiency with absent amylase, diminished trypsin, and normal lipase, we offer a different interpretation than the one presented by the authors. In the light of current information further studies need be done to exclude cystic fibrosis. We doubt whether the findings reported by Lowe and May reflect a static situation as regards pancreatic function. Repeated studies over a period of years may clarify the nature of the defect in their patient. However, the additional test of subjecting the pancreas to a stimulus and studying the pancreatic enzyme response may help determine the presence or absence of cystic fibrosis in this patient, in spite of the normal pulmonary condition. This case and many others, such as those presented in this report, point to the need of a method for diagnosing cystic fibrosis which is not based on pancreatic function. This need was met by the demonstration of the abnormal sweat electrolyte pattern in known patients with cystic fibrosis by di Sant'Agnese [2] and others and the application of this finding as a practical diagnostic test in our laboratory. Our present studies indicate that the sweat test has a high degree of reliability, above

¶Personal communication to the authors.

95%.# These studies include nearly 1000 infants and children, of whom 200 have cystic fibrosis. The usefulness of the sweat test in cases with partial pancreatic insufficiency was reported in October, 1954,[16] when 5 such patients were found to have values of sweat sodium and chloride that corresponded with 53 patients having complete pancreatic deficiency. The recent demonstration by di Sant'Agnese[2] of elevated sweat electrolytes in six patients with partial pancreatic function (reduced trypsin) and of three others with normal pancreatic function (normal trypsin) is in accord with our observations on a total of 23 patients, 13 of whom are included in this report. In the nine cases of di Sant'Agnese trypsin was the only enzyme reported. He presented no evidence of enzyme dissociation, a distinct possibility in spite of a normal or slightly impaired fat and nitrogen balance, and an adequate rise in vitamin A after a test dose.

The data presented in this report are against a hypothesis for this disease which places the initial or primary defect in the pancreas. For many years the concept was championed that in some way the pulmonary involvement was secondary to the pancreatic deficiency, that perhaps a nutritional inadequacy was responsible for the pulmonary changes because of inadequate digestion. It is clear that the pulmonary lesion may appear long before pancreatic enzyme deficiency can be detected by current laboratory tests or by clinical observation. In other words, the severity and extent of the pulmonary lesion is independent of the status of the pancreas. The original hypothesis of Wolbach and Farber of a generalized disease appears sound, with the modification of including a disturbance of the sweat glands as an added and nearly constant feature.

Summary

The results of a long-term study are presented to indicate the occurrence of varying degrees of pancreatic involvement in patients with cystic fibrosis. Four patients succumbed, and the pertinent postmortem findings in these cases are presented. Fourteen additional patients are included, and of these six have been followed sufficiently long by repeated duodenal fluid assays to progress from a state of partial to one of complete pancreatic enzyme deficiency. Dissociation of enzyme activity of the duodenal aspirate is frequently noted in these patients.

In 17 patients the diagnosis of cystic fibrosis was made before complete enzyme deficiency occurred. The features which led to this diagnosis in patients who only had the pulmonary features of cystic fibrosis were positive family history, abnormally increased viscosity of duodenal fluid, scant flow, dissociation of enzyme activity, failure of normal enzyme response to intraduodenal olive oil, loss of enzyme activity in successive tests over a period of months or years, and abnormal gelatin and vitamin A-absorption tests. When the sweat test was developed into a simple, reliable, and practical test, the patients who had been diagnosed as having partial pancreatic insufficiency were recalled for study. In each of 15 patients tested the findings for the sweat sodium and chloride concentration were characteristic of patients with cystic fibrosis having complete pancreatic deficiency. It is estimated that 10% to 15% of all patients with cystic fibrosis present themselves with minimal or no discernable evidence of pancreatic enzyme deficiency. The importance of this finding in relation to theories of pathogenesis as well as the inadequacy of using the duodenal fluid trypsin as a reliable index of the disease are discussed.

Details of more elaborate methods for appraisal of pancreatic status are given. The prognosis in cystic fibrosis does not depend on pancreatic insufficiency but rather on the pulmonary involvement. The recognition of cystic fibrosis in patients with varying degrees of pancreatic involvement

This means that a few patients with known disease have borderline values and still fewer have values which are in the high normal range.

permits the institution of therapy directed toward the pulmonary infection and mechanical obstructive phenomena. We believe this approach accounts for the survival of the majority of patients with extensive pulmonary involvement reported.

Drs. John M. Craig and Sidney Farber aided in and encouraged the above studies.

Miss Barbara Williams provided technical assistance and John Carabitses prepared the illustrations.

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Electrolyte Concentrations in Sweat and Saliva

A Comparison in Patients with Cystic Fibrosis of the Pancreas and Other Conditions

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Studies conducted in our laboratories in connection with the diagnosis of cystic fibrosis of the pancreas in children led us to the comparison of electrolyte concentrations in the sweat and saliva in patients with this disease. The sodium and chloride determination in sweat as performed by di Sant' Agnese * proved to be a very dependable test in diagnosing cystic fibrosis of the pancreas. Chloride concentration above 60 mEq/liter occurred, with but few exceptions, in the sweat of those who had cystic fibrosis of the pancreas. Sodium concentrations presented a greater overlap, but no patients with cystic fibrosis of the pancreas had values of less than 80 mEq/liter. In order to collect sweat the children are placed in a plastic bag for about an hour, as described by Shwachman.[3] Because this procedure is uncomfortable and rather time-consuming, it may not always be easy to perform on older infants and children. Therefore, when S. P. Bessman and his associates reported their findings of high chloride concentration in the saliva of children with cystic fibrosis of the pancreas we began a comparative study of both methods.[4] Bessman found that the presence of more than 30 mEq/liter of chloride in the mixed saliva of these patients indicates cystic fibrosis of the pancreas in the presence of either intestinal or pulmonary signs. To collect sufficient saliva, a small cotton pad is placed in the child's mouth for a few minutes until thoroughly saturated.

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Methods

The sweat was collected and analyzed for chloride and sodium according to the method described by di Sant' Agnese.[2] The saliva was taken as mixed saliva and analyzed for chloride as Bessman and his co-workers suggested.[4] In no instance was the saliva collected immediately after a feeding. We tied a white thread around the small cotton pad which is placed in the patient's mouth. The thread is permitted to dangle from the mouth; this relieves us from holding the pad in the mouth with a forceps and obviates the danger of swallowing or aspirating the pad.

Results

Sweat and saliva tests were done in children with cystic fibrosis of the pancreas and other conditions. We noticed that when the salivary chloride concentration was determined, the results were significantly higher in those under one year as compared with those above one year of age. For this reason we tabulated our results in groups which represented children under and above one year of age. This grouping was done with both sweat and saliva tests, although the electrolytes in the sweat were not influenced by the age of the patient, but apparently only by the presence of cystic fibrosis of the pancreas. Tables 1 and 2 show that children under one year of age who did not

TABLE 1.—*Sweat Test in Children Under One Year of Age with Conditions Other than Cystic Fibrosis of the Pancreas*

Case No.	Age, Mo.	Diagnosis	Sweat, mEq/L.	
			Cl	Na
1	3	Coeliac disease	14.3	9.7
2	10	Malnutrition	25.	30.7
3	3	Pneumonia	4.6	----
4	5	Nutritional anemia	49.	----
5	6	Bronchitis	20.3	18.
6	5	Pneumonia	14.0	29.4
7	6	Asthmatic bronchitis	20.3	18.2
		Mean:	21.1	21.2
		Range:	4.6-49.0	9.7-30.7

have cystic fibrosis of the pancreas have in their sweat an average chloride of 21.1 mEq/liter, and an average sodium of 21.2 mEq/liter, and over one year of age similarly low values, namely, an average 22.4 mEq/liter for chloride and an average 18.4 mEq/liter for sodium. On the other hand, Tables 3 and 4 show that children who did not have cystic fibrosis of the pancreas have in their saliva an average of 44.7 mEq/liter under one year of age and over one year of age, an average of 17.7 mEq/liter of chloride. We were able to compare the electrolyte concentrations of both sweat and saliva in each patient of another group who did not have cystic fibrosis of the pancreas. These results are shown in Tables 5 and 6. In sweat the average chloride concentration for patients under one year of age is 21.6 mEq/liter, and for those over one year of age is 22.5 mEq/liter; under one year of age the sodium is 16.8 mEq/liter and over one year of age is 30.3 mEq/liter. In saliva the average chloride concentration for patients under one year of age in this group was 25.5 mEq/liter, and over one year of age was 12.6 mEq/liter.

Table 7 shows the results of both tests in our patients with cystic fibrosis of the pancreas. In each case there were features of the disease manifest clinically, and laboratory confirmation was obtained by use of the stool trypsin, fat, and starch determinations, vitamin-A alcohol and ester absorption tests, duodenal intubation for trypsin determination and viscosity, and chest

TABLE 2.—*Sweat Test in Children Over One Year of Age with Conditions Other Than Cystic Fibrosis of the Pancreas*

Case No.	Age, Yr.	Diagnosis	Sweat, mEq/L.	
			Cl	Na
8	5	Pneumonia and coeliac disease	59.0	25.0
9	2½	Umbilical hernia	----	40.0
10	4	Nephrosis	8.6	8.3
11	1½	Bronchopneumonia	14.0	11.5
12	13	Hyperthyroidism	32.1	5.3
13	3	Hypothalamic syndrome	3.9	37.6
14	13	Bronchiolitis	5.4	8.9
15	1½	No disease	34.0	10.6
		Mean:	22.4	18.4
		Range:	3.9-59.0	5.3-40.0

TABLE 3.—*Saliva Test in Children Under One Year of Age with Conditions Other Than Cystic Fibrosis*

Case No.	Age, Mo.	Diagnosis	Saliva, mEq/L. Cl
16	9	Diarrhea	21.0
17	8	Hernia	17.2
18	8	Hernia	59.0
19	8 days	Erythroblastosis	98.2
20	9	Congenital heart	18.8
21	1	Diarrhea	93.4
22	6	Bronchopneumonia	25.9
23	2	Diarrhea	56.6
24	4½	Diarrhea	64.2
25	11	Mental retardation	63.7
26	3½	Diarrhea	24.0
27	5	Diarrhea	27.8
28	8	Cyst	36.6
29	5	Bronchitis and pneumonia	20.0
		Mean:	44.7
		Range:	17.2-98.2

TABLE 4.—*Saliva Test in Children Over One Year of Age with Conditions Other Than Cystic Fibrosis of the Pancreas*

Case No.	Age, Yr.	Diagnosis	Saliva, mEq/L. Cl
30	4	Schönlein's purpura	13.7
31	6	Hernia	16.4
32	6	Burns; plastic surgery	12.5
33	3	Hydronephrosis	12.7
34	2½	Rheumatoid arthritis	33.0
35	6	Post poliomyelitis	20.3
36	2	Tonsillitis	22.0
37	4	Diarrhea and pneumonia	5.6
38	6	Bronchopneumonia	20.5
39	7	Post poliomyelitis	20.8
40	2	Post poliomyelitis	32.6
41	8	Myasthenia gravis	9.1
42	8	Cystitis	21.0
43	8	Sickle cell anemia and tonsillitis	20.8
44	8	Cystitis	16.0
45	6	Appendectomy; mental retardation	14.3
46	13	Asthma	10.0
		Mean:	17.7
		Range:	5.6-33.0

TABLE 5.—*Comparison of Sweat and Saliva Test in Children Under One Year of Age with Conditions Other Than Cystic Fibrosis of the Pancreas*

Case No.	Age, Mo.	Diagnosis	Sweat, mEq/L.		Saliva, mEq/L.
			Cl	Na	Cl
47	11	Diarrhea	24.0	2.9	34.0
48	4	Diarrhea	3.1	4.4	30.8
49	5	Bronchopneumonia	10.9	17.4	17.2
50	4½	Diarrhea	15.0	9.9	27.5
51	1	No disease	37.4	49.6	32.6
52	3	Gastroenteritis	52.3	34.5	21.0
53	1	Diarrhea	11.9	11.8	35.0
54	9	Pneumonia	22.9	7.8	10.6
55	4	Diarrhea	8.5	7.6	15.5
56	3	Diarrhea	20.1	10.6	11.3
57	11	Bronchitis	54.2	57.6	21.1
58	12	Chronic diarrhea	8.8	14.3	13.4
59	11 days	Diarrhea	3.1	4.4	55.8
60	2	Bronchitis	7.3	12.2	9.6
61	5	Bronchopneumonia	16.0	10.2	31.0
62	2	Pneumonitis	49.4	17.0	41.3
		Mean:	21.6	16.8	25.5
		Range:	3.1-54.2	2.9-57.6	9.6-55.8

TABLE 6.—*Comparison of Sweat and Saliva Test in Children Over One Year of Age with Conditions Other Than Cystic Fibrosis of the Pancreas*

Case No.	Age, Yr.	Diagnosis	Sweat, mEq/L.		Saliva, mEq/L.
			Cl	Na	Cl
63	1½	Bronchopneumonia	34.0	10.6	9.0
64	2	Abscess	14.1	18.8	11.3
65	7	Bronchopneumonia	12.6	50.0	20.4
66	4	Rectal prolapse	29.6	52.9	16.4
67	1½	Diarrhea	18.9	20.4	18.6
68	2	Recurrent pneumonia	11.1	14.3	12.3
69	1½	Bronchopneumonia	32.8	55.3	6.2
70	3	Pneumonia	11.6	14.5	10.2
71	6	Malnutrition	37.4	36.0	9.0
		Mean:	22.5	30.3	12.6
		Range:	11.1–37.4	10.6–55.3	6.2–20.4

roentgenograms. The mean sweat chloride was 107 mEq/liter, with a range of 71.0 mEq/liter to 186 mEq/liter; sodium ranged from 77 mEq/liter to 197.6 mEq/liter, with a mean of 111.3 mEq/liter; salivary chloride ranged from 17 mEq/liter to 87.1 mEq/liter, with a mean of 29.9 mEq/liter.

TABLE 7.—*Comparison of Sweat and Saliva Test in Children with Cystic Fibrosis of the Pancreas*

Case No.	Age, Yr.	Sweat, mEq/L.		Saliva, mEq/L.
		Cl	Na	Cl
72	5	85.2 71.0	115.9 ----	20.0 20.6
73	1	129	123.0	33.5
74	2½	81.3	84.3	----
75	9	----	77.0	24.1
76	7	100.2	155.0	17.0
77	2	131.0	133.6	----
78	1½	186.0	197.6	48.0
79	13	68.9	77.2	18.5
80	6 wk.	110.7	78.0	87.1
		Mean: 107.0	111.3	29.9
		Range: 68.9–186.0	77.0–197.6	17–87.1

Comment

All the patients with cystic fibrosis of the pancreas had significantly higher levels of electrolytes in the sweat. The salivary chlorides tended to be higher in those patients with cystic fibrosis of the pancreas; however, there was considerable discrepancy, as can be seen by comparing the data in Tables 3 to 6 with Table 7. Another finding of significance, as may be seen by comparing Tables 3 and 4 is that the saliva test gave higher results in patients below one year of age as compared with those above. In fact, the highest values were in the youngest infants. This is well demonstrated in Tables 3 and 5. In Table 3 values of above 90 mEq/liter occurred in the youngest children, Case 19, age 8 days, and Case 21, age one month. And in another group, Table 5, in which the sweat and saliva tests were compared in the same patient, the highest value is that of the youngest child, Case 59, age 11 days. The influence of age is manifested also in the group with cystic fibrosis of the pancreas. In Table 7 the youngest child with cystic fibrosis, Case 80, 6 weeks of age had the highest saliva value, 87.1 mEq/liter. One may speculate as to whether there is a physiological difference in the functioning of the salivary glands in infancy, and we intend to pursue this problem further in proposed studies.

Measurement of electrolyte concentrations in the sweat has been shown to be an excellent diagnostic test in cystic fibrosis

of the pancreas and is of value in any age group. It also is unique among all the tests in that it may detect this disease in the absence of intestinal symptoms. It has been estimated that 10% of patients with cystic fibrosis of the pancreas may not exhibit pancreatic dysfunction at some time in the course of their disease.[5] Although the saliva test in general yields higher values in those with cystic fibrosis of the pancreas, it does not give consistent results. Therefore, it is not dependable, and this is particularly important in infants below one year of age when early diagnosis and treatment are necessary. Furthermore, there is a significant discrepancy in other age groups as well. Therefore, we must conclude that, in its present form, the saliva test does not offer substantial aid in diagnosis. Perhaps as knowledge of the physiology of the salivary glands in infancy is advanced, the reasons for this will become more clear and modifications can then be introduced. For the present, however, the sweat test remains the best available test in this disease.

Conclusions and Summary

Electrolyte determinations in sweat and saliva were compared in children with and without cystic fibrosis of the pancreas. The sweat test was shown to be a reliable and accurate diagnostic measure. However, the saliva test did not provide consistent results, and thus cannot be considered an accurate test in the diagnosis of cystic fibrosis of the pancreas.

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The Electroencephalogram and Various Aspects of Mental Deficiency

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The relationship between the electroencephalogram and the intelligence level has been studied by many authors. In recent years, with increasing knowledge of the types of tracing seen in normal children, it seemed pertinent to review a new group of cases.

A great deal of the early work was done by Kreezer* and by Kreezer and Smith. This work was primarily concerned with the relationship between mental age and various attributes of the alpha rhythm, such as frequency, amplitude, and alpha index. The results were suggestive of a relationship between development of alpha and intelligence, but they were not clear-cut.

Studies by Rahm and Williams, Knott, Friedman and Bardsley, and Gunnarson have also failed to reveal any definite change characteristic of mental deficiency. Other authors, Putnam and Merritt, Posey, and Cook, have discussed in detail the relationship between mental deficiency and epilepsy. That there is a close connection between these two conditions has been well recognized (Keith, Ewert, Green, and Gage), and in a recent study Stotijn has gone into this problem at length. He made the point that it is very difficult to diagnose petit mal in low-level oligophrenics. In his study he obtained a group of 43 "standard" oligophrenics from a group of retarded patients by eliminating the following groups of patients: "a. Patients with clinical symptoms of epilepsy and those with paroxysmal activity in the EEG. b. Patients with mongoloid idiocy and complicating disturbances as schizophrenia, congenital blindness or deafness, and degenerative diseases of the nervous system. c. Patients younger than 16 years." Note that, as well as discarding patients with clinical epilepsy, he also discarded those patients who had paroxysmal activity in the electroencephalogram. Using a six-channel electroencephalograph and monopolar and bipolar leads with photic stimulation, he found in this "standard" group little relationship between developmental level and the electroencephalogram. A partial exception was a group of records showing "low voltage irregular activity" in the most retarded patients.

Selection of Material

Our study is of a consecutive series of retarded patients, including children, who have undergone a complete examination at the Mayo Clinic over the last three years. All these patients showed the clinical picture of mental retardation, and this has been confirmed by intelligence testing. The only retarded patients not included were those in whom any history was obtained at any time of epilepsy; that is, a history of spells of jerking, unconsciousness, or localized movements. The history appears to be the only way (at least in outpatients, as the great majority of our patients were) that one can exclude clinical epilepsy, and it means that one has to rely more or less completely on a very careful interview with the patient and his parents; or, to express it another way,

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*References 7 and 8.

one has to rely on the memory and powers of observation of the patient's family.

All patients underwent a complete physical examination, and, if indicated, special examinations were done in the sections of Ophthalmology, Otorhinolaryngology, or Neurology. All patients had an intelligence test given by a staff psychologist.† One of the following tests was used: Cattell Infant Intelligence Scale, Vineland Social Maturity Scale, Stanford-Binet Form L, Wechsler Intelligence Scale for Children, or the Wechsler-Bellevue Adult Intelligence Scale. Only those patients were included who, in addition to the foregoing, had satisfactory electroencephalographic recordings. A total of 74 patients fulfilled these criteria. Forty-six were male and twenty-eight were female. Their intelligence quotients (or social quotients on the Vineland Scale) ranged from 15 to 75. Their ages ranged from 8 months to 21 years; 69 of them (93%) were less than 16 years of age.

Physical Classification

The majority of the patients came under the category of primary undifferentiated amentia, Tredgold's simple amentia. In addition, there was one child with the classic picture of mongolism and two other children who probably showed this picture. There was one microcephalic ament who was also spastic.

In any group of mentally retarded patients it is common to find a wide range of other physical conditions. In our group of 74 patients, 9 patients, all children, had a greater or lesser degree of spasticity of the limbs; 2 had greatly reduced hearing as shown by audiogram. One patient was thought to have congenital aphasia, another cortical blindness, and another a localized cortical lesion. One child was a severe breath-holder; he frequently held his breath until he became cyanotic. Three patients, all children, were so seriously disturbed emotionally as to be considered schizophrenic. In this connection one must comment on the difficulty of differentiating between an autistic withdrawal in an intelligent child on the one hand and a retarded child on the other hand. In order to make this distinction one may need to study the entire family intensively, using the collaborative technique. In other children the two conditions may coexist. We felt that true retardation was present in all of our three emotionally disturbed children, in addition to the emotional difficulty.

One child showed some of the features described by Fanconi—congenital malformations and hypoplastic anemia—and another was thought to have a gait compatible with myelodysplasia. One child gave the picture of oxycephaly. Another child showed the following group of findings: mental retardation, cerebellar and extrapyramidal signs, telangiectasis of the sclera, and possibly scleroderma. Three children had a history of encephalitis in infancy; one other child in addition had had an occipital encephalocele removed in infancy.

Behavioral Classification

In addition to the study of the physical and intellectual status of these patients, an attempt was made to record their characteristic behavior patterns as reflected in their motor activity. That is, we tried to divide them into (*a*) those who were very active, difficult, or uncontrollable—a group corresponding in some respects to the hyperkinetic children of Ounsted; (*b*) those who behaved more or less like the average for that particular age, and (*c*) those who were unusually passive, quiet, and docile. This classification was done on the basis of a careful historical review and of our observation of the patient at the time of each of his various examinations here. Since these examinations were done over several days and by at least three groups of people, the clinicians, the psychologists, and the personnel of the electroencephalographic laboratory, a fairly clear picture of the characteristic behavior patterns of the patient could usually be obtained.

Electroencephalographic Technique

The records were made while the patient was sitting, or held in the mother's lap. Sedation was not used, it being found that, with care, the children cooperated satisfactorily. However, it was not possible in all cases to obtain satisfactory tracings with the eyes closed, or during hyperventilation. Fourteen disk electrodes held in place with collodion were placed as follows: Ten were in two parasagittal rows, 1 to 1½ in. from the midline, and spaced evenly between the frontal and occipital regions. A sylvian electrode was placed on each side of the head vertically above the external auditory meatus, and an ear electrode was placed on the lobe of each ear. Recordings were made from various combinations of these electrodes, using both bipolar and monopolar techniques, on an eight-channel Grass electroencephalograph.

Results

Electroencephalographic Data.—The records were examined visually with the following features in mind: (1) the presence or absence of abnormal waves, (2) the

†The tests were given by Mrs. Josephine Ewert, Mrs. Meredith Green, and Dr. William Seeman.

maturity for age of the record, and (3) the response to photic stimulation. These data were then classified within each of the following categories:

1. Note was made of the presence or absence of abnormal waves. The accepted range of normality for each group followed that described by Corbin and Bickford. The abnormal waves were descriptively either (*a*) in the delta frequency of ½ to 3 cps., or (*b*) in the range of dysrhythmic activity —abnormal waves of 4 cps. or more (mostly in the theta range of 4 to 7 cps.) and including the wave forms characteristic of epilepsy. Each of these abnormal wave forms could be either focal or general, symmetrical or asymetrical.

Only two patients showed abnormal activity in the delta range (that is, persistent ½ to 3 cps. arrhythmic activity relatively unaffected by eye opening). In both cases the abnormality was minimal, and both patients probably had cortical damage.

The records showing dysrhythmic activity arranged themselves into three grades. In dysrhythmia, grades 1 and 2, the activity was nonspecific and mostly within the theta (4 to 7 cps.) range. It tended to be rhythmic and repetitive, and tended to be inhibited by eye-opening and accentuated by hyperventilation. It was usually of less than 60 microvolts amplitude. In the group of patients under study this type of activity was often confined to one head area.

The records read as dysrhythmia, Grade 3, showed either typical focal or general spikes, or sharp waves, or the spike-and-wave pattern commonly associated with petit mal. In some records both of these abnormalities were seen together.

In addition three records showed no abnormal waves but did show marked asymmetry (greater than 25%) of the alpha rhythm.

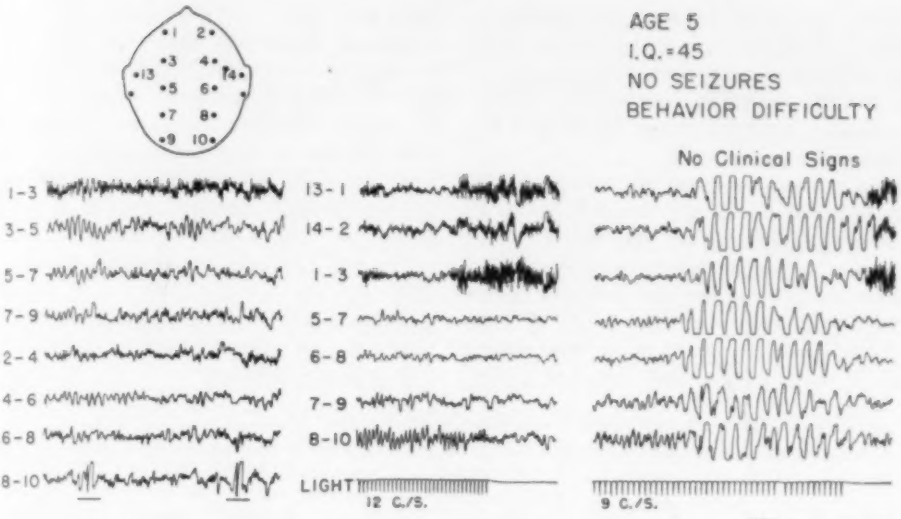
2. An estimation was made by visual analysis of the maturity of the background activity for the particular age group of the patient. This was done by reference to the work of Henry and to the scattergrams of Corbin and Bickford's Study. In this study electroencephalograms of a group of children of all ages between 1 and 10 years were recorded within a month of their birthday. The records were analyzed by a Walter automatic frequency analyzer. The various records in each age group were then presented as a scattergram showing the contrast between the slower, more immature records on the one hand and the faster, more mature records on the other. In our study each record was analyzed visually for maturity with reference to these scattergrams. Those with a preponderance of slow activity below the limits of the study referred to previously were recorded as immature for age. Those within the limits of that study were recorded as within the average limits for that age. Those records with a preponderance of faster, more mature activity, above the limits of the study, were recorded as mature for age.

3. In 70 of the 74 patients photic stimulation was given. The response to light was recorded as follows: (*a*) no response, (*b*) minimal to moderate driving, (*c*) good driving, and (*d*) light-sensitivity with light-triggered paroxysmal activity. Only the last category (*d*) is considered abnormal.

The figure illustrates the type of abnormality (dysrhythmia, Grade 3) typically found.

The crude results are as follows. There were 30 records essentially normal (40.5%); 30 showed dysrhythmia, Grade 1 or 2 (40.5%); 9 showed dysrhythmia, Grade 3 (12%); there were 2 records with delta (3%) and 3 showing asymmetry (4%). This electroencephalographic abnormality rate is consistently higher than is found in the normal population, although it is difficult to find an entirely comparable group. For instance, Corbin and Bickford reported a 4% incidence of dysrhythmia, Grade 3, in normal children.

Concerning the background activity 43 were classified as of average maturity (60%). Nine were relatively immature (13%) and nineteen were mature (27%).



Mental retardation with gross electroencephalographic abnormality. Note focal occipital sharp wave (underlined in bottom trace), asymmetric driving response (maximal on right) and diffuse paroxysmal discharge with photic stimulation. Child active and difficult to manage, clumsy in movements. Air encephalogram: slight hydrocephalus.

(In three records these data were not recorded.) Thus no significant evidence was found of delayed maturation of the cortical rhythms, this being consistent with the findings of other workers. Twenty gave no response to photic stimulation (29%). Twenty-one gave minimal to moderate driving (30%), seventeen good driving (24%), and twelve a paroxysmal response (17%). (In four records these data were not recorded.)

Sleep.—One patient was drowsy throughout the recording, and the high voltage, 5 to 6 cps. activity, sometimes seen in this stage of sleep in children, was present throughout.

In three patients records were made during actual sleep. In two of these an abnormality previously present in the waking record disappeared. In one of these cases the abnormality was a dysrhythmia, Grade 1, localized to the posterior head regions, and in the other there was an asymmetry of the alpha rhythm.

Structural Central Nervous System Disease.—It has been mentioned that several patients had, in addition to mental deficiency, structural abnormalities of the central nervous system. These patients are among those referred to previously; there were 20 in all in whom we believed that structural central nervous system disease probably existed. Ten of these were spastic children (one of whom had microcephaly in addition), there was one mongol, and two probable mongols. One child was aphasic, one blind with an enlarged sella, one had a probable cortical lesion, and another a probable cerebellar lesion. In another patient an occipital encephalocele had been removed in infancy. There was one case with some of the features of the Fanconi syndrome and one case of oxycephaly.

Of the records in these 20 cases, 8 (40%) were normal. Six (30%) showed dysrhythmia, Grade 1 or 2, and two (10%) showed dysrhythmia, Grade 3. In addition, two (10%) showed asymmetry of the alpha, and two (10%) showed a delta, Grade 1. These figures are not remarkably different from the results for the whole group. The only exception is that of the five records in the entire series of 74 patients showing

either asymmetry of the alpha rhythm or delta activity, four are in this smaller group of 20 patients with organic disease referable to the central nervous system. But the percentage of dysrhythmia, Grade 3, is less than in the entire series.

In this smaller group the maturity of the records was scored as follows: Five (26%) were immature for the age; seven (37%) were of average maturity, and seven (37%) were mature for the age. (In one patient these data were not recorded.) In comparison with the entire group these figures show more mature and immature recordings, especially the latter, and somewhat fewer average records.

In seven (37%) there was no response to photic stimulation, in six (32%) minimal to moderate driving, in five (26%) good driving, and in one (5%) there was a paroxysmal response. (In one case photic stimulation was not performed.) In comparison with the entire group these figures show more patients with no response to photic stimulation, and fewer patients with a paroxysmal response. These figures indicate that clinically demonstrable structural central nervous system disease does not entirely account for the observed electroencephalographic abnormality.

Intellectual Development.—To investigate the correlation between intellectual development and the electroencephalogram, two groups of 25 patients each were selected. In one group were the 25 patients with the highest intelligence quotients; all were above 57. In the other group were the 25 patients with the lowest intelligence quotients; all were below 38. A comparison was made of the electroencephalographic records in each group, for (1) abnormal waves, (2) maturity, and (3) response to photic stimulation.

Abnormal Waves: In Table 1 the incidence of dysrhythmia, Grade 3, in the low I.Q. group is well seen.

TABLE 1.—*Distribution of Abnormal Waves*

	Total	Normal	Dysrhythmia		Delta	Asymmetry
			Grades 1 and 2	Grade 3*		
High I. Q. group	25	10	13	1	1	0
Low I. Q. group	25	7	10	6	1	1

*Difference between groups statistically significant at level ≦0.05.

Background Activity: As has been mentioned, the records were classified as follows: immature for age, of average maturity, and mature for age (Table 2). There is little difference between the two I.Q. groups. This suggests that there is no definite correlation between the amount of intellectual retardation and the maturity in the electroencephalogram. This is in agreement with previous work.

Photic Stimulation: Here again each record was scored as follows: no response, minimal to moderate driving, good driving, and light-sensitive with triggering of paroxysmal activity (Table 3). Both the higher rate of light-sensitivity in the low I.Q. group and the higher rate of good driving in the high I.Q. group are well seen. While

TABLE 2.—*Distribution of Background Activity*

	Total	Immature	Average	Mature	Data Not Recorded
High I. Q. group	25	3	16	5	1
Low I. Q. group	25	5	14	5	1

TABLE 3.—*Response to Photic Stimulation*

	Total	No Response	Minimal to Moderate Driving	Good Driving	Light-Sensitive (Paroxysmal Response)	Data not Recorded
High I. Q. group	25	6	7	8	3	1
Low I. Q. group	25	6	8	3	7	1

there remains some doubt as to the clinical significance of photically induced paroxysmal discharges when the latter are not associated with clinical manifestations (petit mal, and so forth), their occurrence in these cases, and especially in the low I.Q. group, would certainly raise the question of a relationship to epileptic disorders.

Behavior Patterns.—We selected two groups: the 18 most active, uncontrollable, difficult (hyperkinetic) children, and another group of the 18 most passive, quiet, docile children.

Abnormal Waves: Although the numbers in Table 4 are small, there seems to be a significantly higher proportion of children with normal records in the quiet, docile group, and a significantly higher proportion of dysrhythmia, Grade 3, records in the active, difficult group.

Background Activity: The relative maturity of the records was as shown in Table 5. Here there seems to be little difference between the groups.

Photic Stimulation: It can be seen from Table 6 that the triggering of a paroxysmal response to a flashing light occurred much more frequently in the active, difficult children than in the passive group and also that a good driving response is seen more frequently in the passive, docile children than in the active group.

TABLE 4.—*Distribution of Abnormal Waves*

	Total	Normal	Dysrhythmia		Other
			Grades 1 and 2	Grade 3*	
Active, difficult group	18	5	9	4	0
Passive, docile group	18	9	8	0	1

*Difference between groups statistically significant at level ≤ 0.05.

TABLE 5.—*Distribution of Background Activity*

	Total	Immature	Average	Mature
Active, difficult group	18	1	13	4
Passive, docile group	18	3	11	4

Comment

It may seem surprising that our results, in part confirming the work of others, indicate that there may be no detectable electroencephalographic abnormality in patients with gross intellectual defect. However, those familiar with the nature of recordable electroencephalographic activity from the scalp might have predicted such a result. There is, indeed, only a very loose relationship between changes in the electroencephalogram and mental activity, and whenever a relationship can be demonstrated—for example, the inhibition of alpha rhythm during calculation—it is usually negative in

TABLE 6.—*Response to Photic Stimulation*

	Total	No Response	Minimal to Moderate Driving	Good Driving*	Light-Sensitive (Paroxysmal Response)	Data No Recorded
Active, difficult group	18	6	5	1	5	1
Passive, docile group	18	4	7	6	1	0

*Difference between groups statistically significant at level ≤ 0.05.

direction. Occasionally, however, positive correlations are encountered, as in those epileptic patients in whom various types of mental activity may induce seizure discharges.

On the other hand, electroencephalographic rhythms are very sensitive to changes in the awareness of the subject, and this observation has led to the suggestion that although the spontaneous rhythms of the scalp electroencephalogram may have a regulatory function in relation to consciousness, they are not implicated in other higher intellectual functions. Also, it is possible that in intellectually deficient patients the primary defect is not cortical in location and hence it may require depth electrographic studies before the neuronal anomaly can be found.

In contrast to the foregoing findings is the observation that gross electroencephalographic abnormalities, when present in our patients, occurred in the lower-grade defectives and, in particular, in those children in whom there was evidence of hyperkinetic behavior. This observation is of particular interest in relation to the findings of Ounsted, who demonstrated rather gross electroencephalographic abnormalities in a selected group of epileptic children with hyperkinetic behavior. This suggests, as would be expected on clinical grounds, that our material is not homogeneous and that the patients with more abnormal electroencephalographic findings may be a subgroup with an underlying pathologic picture more nearly related to that of the epilepsies. However, it is also arguable that these patients may be potential epileptics who have not yet manifested seizures or whose seizures, if they have occurred, have been missed or misinterpreted by their parents.

Whichever of the foregoing explanations is favored in any particular instance, there would seem to be a good case to be made for a trial of anticonvulsant medication in these hyperkinetic children.

Summary

Seventy-four patients (93% of them less than 16 years of age) were selected for electroencephalographic examination because of the presence of mental retardation and the absence of clinical epilepsy.

In the entire group the electroencephalograms were normal in 40.5%, showed dysrhythmia, Grade 1 or 2, in 40.5% and dysrhythmia, Grade 3, in 12%. The records were classified as immature for age in 13%, of average maturity in 60%, and mature for age in 27%. There was no response to photic stimulation in 29%, minimal to moderate driving in 30%, good driving in 24%, and a paroxysmal response in 17%.

A group of patients selected because they were less retarded than the series as a whole showed slightly more normal records and more records with a good driving response. A contrasting, more retarded group showed definitely more records with a dysrhythmia, Grade 3, pattern and also more records with a paroxysmal response to photic stimulation. The electroencephalograms of these two groups showed essentially the same level of maturity.

Another group selected because of active, uncontrollable, or "hyperkinetic" behavior showed somewhat fewer normal records, more dysrhythmia, Grade 3, activity and a

markedly higher number of paroxysmal responses to light when compared to an equal group of quiet, easily managed children.

The significance of these abnormalities in the hyperkinetic children and the possible relationship of this syndrome to epilepsy are discussed. The suggestion is made that anticonvulsant medication may be helpful.

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Pyridoxine Hydrochloride (Vitamin B_6) Need in Infants and Children

A Study in Patients with Anemia, Convulsions, and Acute Infections

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The clinical manifestations of pyridoxine deficiency in infants have been described in recent reports. Snyderman and co-workers[1] noted the occurrence of microcytic, hypochromic anemia in one and convulsions in the second of two infants maintained on a diet deficient in pyridoxine hyrdochloride for a prolonged period of time. The clinical manifestations were improved by adding pyridoxine hydrochloride to the basal diet. Convulsions occurred in a group of infants fed milk mixtures deficient in pyridoxine hydrochloride according to reports by Coursin[2] and Moloney and Parmelee.[3] This symptom did not recur when the diet contained adequate amounts of pyridoxine hydrochloride. It is noteworthy that the infants reported in detail were all under 3 months of age, save for the two children reported by Snyderman, who were 8 months and 2 years of age, respectively.

Stimulated by these reports we have sought evidence of pyridoxine need in a small group of boys between the ages of 5 months and 4 years who were hospitalized because of convulsions or severe anemia. Another group of hospitalized children of similar age and sex but with acute infectious diseases was also studied for comparison with the first group. Evidence of pyridoxine need was determined by quantitative determination of urinary xanthurenic acid and N^1-methylnicotinamide excretion before and after ingestion of a standard dose of DL-tryptophan. In some patients quantitative estimations of the urinary excretion of xanthurenic acid and 4-pyridoxic acid were determined before and after intramuscular pyridoxine hydrochloride plus DL-tryptophan load.

The use of the three methods for deriving evidence of pyridoxine deficiency in humans is predicated upon the following observations. Vitamin B_6 is necessary for the complete metabolism of tryptophan to nicotinic acid.[1] An intermediary product in this metabolic transformation is xanthurenic acid (XA). Although some XA occurs in the urine of normal adults after a tryptophan load (4 to 30 mg. in 24 hours),[4] little or no XA is excreted in the urine of normal milk-fed infants following a standardized load of DL-tryptophan.[5] Adult patients thought to have pyridoxine deficiency excreted a larger amount of XA in the urine than normal patients following a tryptophan load,[4] but quantitative data on this point in infants with pyridoxine deficiency are not available.[5] In both adults and infants administration of pyridoxine resulted in either a marked reduction or disappearance of XA from the urines of those patients suspected of having pyridoxine deficiency.*

N^1-methylnicotinamide (NMN), a nicotinic acid derivative, occurs normally in the urines of healthy infants and adults.† After the administration of from 2 to 5 gm. of DL-trypotophan, the 24-hour excretion of NMN is increased from 1.2 to 6 times the

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* References 4 and 5.

† References 6 and 7.

control values.‡ In the presence of pyridoxine deficiency in the infant, administration of from 0.19 to 0.26 gm/kg. of L-tryptophan resulted in no increase in the urinary NMN.[1] Snyderman and associates felt this test to be a most sensitive indication of vitamin B_6 deficiency in the infant.

The predominant metabolite of vitamin B_6 excreted in the urine is 4-pyridoxic acid (4-PA).[8] Adults on a self-selected diet excrete from 0.6 to 11.1 mg. in 24 hours.§ Starved adults excrete from 0.2 to 1.8 mg/day. The two infants studied by Snyderman excreted from 0.2 to 0.6 mg. a day while receiving a diet containing 0.67 mg. of pyridoxine a day. When the pyridoxine was omitted from the diet, one infant ceased excreting 4-PA immediately, the second infant, in 40 days. After a 50-mg. dose of pyridoxine one infant excreted 3.4 mg. of 4-PA during the subsequent 24-hour period.

Methods and Materials

Three groups of hospitalized children were studied. All were boys less than 4 years of age. The first group was children with hypochromic, microcytic anemia. The type of anemia was determined by the use of blood indices plus examination of the peripheral smear by the chief pathologist, Dr. Thomas Hepler. The second group of children had convulsions. The third group of children had acute infectious diseases of varying severity. After admission a urine-collecting tube was taped to the infant or child and a 24-hour specimen was collected. This is referred to as Period-I urine. At the beginning of the second 24-hour period, DL-tryptophan in a total dose of 0.54 gm/kg. was given by mouth or gavage tube in two divided doses at 4-hour intervals, and the second 24-hour urine collection was completed. This was Period-II urine. In selected instances pyridoxine hydrochloride, 25 mg., was then given in one intramuscular dose on two successive days. At the beginning of the ensuing or fifth 24-hour period, DL-tryptophan, 0.54 gm/kg. was given in two divided doses as on the second day, and a final 24-hour urine specimen was collected. This was Period-III urine.

During the study the children received only water and electrolytes orally or intravenously or, in the case of mildly ill children, a cow's-milk diet containing no more than 80 Cal/kg. and no vitamin supplements. All urines were collected in four six-hour aliquots in amber bottles containing toluene. After collection the urines were pooled to form 24-hour specimens, the total volume was measured and aliquots were then stored at icebox temperature until determinations were completed.

XA was determined by the colorimetric method of Wachstein and Gudaitis with the use of a Coleman Jr. Spectrophotometer.[9] The NMN determinations were done using the method of Huff and Perlzweig.[7] Fluorescence was measured with the Coleman Model 12C photofluorometer using PC-1 and B-1 filters and the AH-3 mercury-vapor lamp. The determination of 4-PA was by the fluorescent method of Huff and Perlzweig[10] as modified by Sarett.[8] Concentrations of 4-PA were determined as the lactone from a standard curve derived from a heated solution of 4-PA in 0.1 normal HCl diluted with a sodium borate buffer.‖ Calibration of the photofluorometer for both NMN and 4-PA determinations was performed against quinine sulfate in 0.1 normal H_2SO_4. All determinations were done by the same person (M.P.).

In reporting the results one value is expressed as "less than—milligrams." In this instance the amount of substance in an undiluted urine specimen was lower than the lowest point on the straight-line portion of the standard curve of concentrations for that substance.

Repeated determinations (18) of XA on one urine specimen indicated a coefficient of variation for the method of 4.8%. There was no evidence of deterioration of the XA on storage. The coefficient of variation for repeated determinations (20) of NMN on one urine specimen was 8.7%. There was no deterioration of NMN on storage. The coefficient of variation for the repeated determination (12) of the 4-PA values on one urine specimen was 20.6%. A large amount of fluorescence often appeared in the untreated urine, indicating the presence of a high amount of interfering substances in the photofluorometric determination of 4-PA.

‡ L-Tryptophan is the only form giving rise to N^1-methylinicotinamide in urine (Reference 6) However, it is best from an economic viewpoint to use DL-tryptophan which contains equal amounts of the dextro- and levo-rotatory isomers of tryptophan.

§ The method of measurement of 4-PA in the urines of patients on a self-selected diet must include unspecific fluorescence besides 4-PA, and this accounts for an obvious excess of 4-PA excretion over any reasonable estimate of the B_6 intake. This, however, does not seem to invalidate the retention data obtained when a large load of B_6 is employed and urinary 4-PA is measured.

‖ Dr. Augustus Gibson, of Merck & Co., Inc., Rahway, N. J., supplied the 4-pyridoxic acid.

TABLE 1.—*Summary of Clinical and Laboratory Data in Patients with Acute Infectious Diseases*

Patient	Age, Mo.	Weight, Kg.	Body Surface, M^2	Diagnoses	Urinary Excretion, Mg/24 Hr.				Increment Index*	
					Collection Period†	XA‡	NMN§	4-PA‖	NMN§	4-PA‖
1	5	7.2	0.35	Gastroenteritis, infectious; intussusception, postoperative	I II	2.4 13.1	4.8 8.8	---- ----	1.8	----
2	6	8.2	0.38	Gastroenteritis, infectious; dehydration, moderate	I II III	0 0 0	0.9 4.1 ----	0.41 ---- 1.40	4.5	3.4
3	8	9.0	0.40	Gastroenteritis, infectious; dehydration, severe	I II	0 0	3.4 4.1	---- ----	1.2	
4	9	9.6	0.42	Gastroenteritis, infectious; dehydration, mild	I II III	0 0 0	0.8 1.9 ----	<0.48 ---- 1.50	2.4	?
5	11	9.8	0.42	Streptococcosis; bronchitis; diarrhea, parenteral	I II III	0 15.0 0	2.2 4.5 ----	0.54 ---- 1.70	2.0	3.2
6	17	10.1	0.44	Congenital heart disease, cyanotic type; subacute bacterial endocarditis	I II	0 76.0	0.7 1.9	---- ----	2.7	
					5-wk. interval, diet—milk, solids, no added pyridoxine					
					I II III	0 48.0 8.2	1.5 3.5 ----	0.35 ---- 3.30	2.3	9.4
7	30	12.5	0.54	Meningitis and septicemia due to H. influenza	I II	0 78.0	5.9 2.2	---- ----	−2.7	
8	32	13.6	0.57	Ulcerative stomatitis, recurrent, etiology?	I II	3.1 6.3	3.0 7.8	---- ----	2.5	
9	42	15.9	0.63	Synovitis, hip, acute, nonbacterial	I II III	0 15.0 0	1.8 7.0 ----	1.3 ---- 4.1	3.9	3.2

* Increment Index—For N¹-methylnicotinamide—milligrams Period II/milligrams Period I.
For 4-Pyridoxic Acid—milligrams Period III/milligrams Period I.

† Collection Period: I—Control.
II—Following *DL*-tryptophan, 0.54 gm/kg., orally.
III—Following pyridoxine HCl., 25 mgs. per day intramuscularly for two days, then *DL*-tryptophan, 0.54 gm. per kg., orally.

‡ Xanthurenic Acid.
§ N¹-methylnicotinamide.
‖ 4-Pyridoxic acid.

‡ Xanthurenic Acid.
§ N¹-methylnicotinamide.
‖ 4-Pyridoxic acid.

TABLE 2.—*Summary of Clinical and Laboratory Data in Patients with Anemia and Convulsions*

Patient	Age, Mo.	Weight, Kg.	Body Surface, M²	Diagnoses	Urinary Excretion, Mg/24 Hr.				Increment Index*	
					Collection Period†	XA‡	NMN§	4-PA‖	NMN§	4-PA‖
10	12	9.5	0.42	Anemia, hypochromic, microcytic. Hgb.-5.5 grams. Convulsions, febrile. Bronchitis, infectious.	I II	0 4.1	1.8 2.0	---- ----	1.1	
11	15	10.9	0.43	Anemia, hypochromic, microcytic. Hgb.-5.4 grams. Septicemia due to staphylococci.	I II	0 13.0	4.0 6.4	---- ----	1.6	
12	16	9.4	0.44	Anemia, hypochromic, microcytic. Hgb.-4.5 grams.	I II	0 0	1.8 4.3	---- ----	2.4	
13	17	10.9	0.44	Anemia, hypochromic, microcytic. Hgb.-2.5 grams. Cardiomegaly secondary to anemia.	I II III	0 5.0 0	1.6 4.6 ----	0.61 ---- 1.10	2.9	1.8
14	13	10.8	0.47	Convulsions with mental retardation. Cerebral dysrhythmia, Fast-2.	I II III	0 0 0	1.4 3.5 ----	0.60 ---- 1.70	2.5	2.8
15	17	10.7	0.48	Convulsions due to fever. Nasopharyngitis.	I II	0 8.2	1.8 8.6	---- ----	4.8	
16	30	10.9	0.50	Convulsions due to fever. Nasopharyngitis. Cystitis, acute.	I II	0 4.7	1.5 3.4	---- ----	2.3	
17	42	15.9	0.66	Convulsions due to fever. Pyelonephritis.	I II III	0 10.0 0	1.9 2.5 ----	2.5 ---- 8.5	1.3	3.3

For an example of symbols see Table 1.

Results

The 24-hour urinary excretions of XA and NMN in 17 patients and of 4-PA in 8 patients are tabulated in Tables 1 and 2. Pertinent clinical data are included for each patient. XA was found in Period-I urines of 2 patients in amounts of 2.4 and 3.1 mg., respectively, and was absent from Period-I urines of 14 patients. The average XA excretion for all patients in Period-I urine was 0.3 mg. XA was found in Period-II urines in 12 patients in amounts ranging from 5 to 78 mg. (average, 22.8 mg.). Five patients excreted no XA in Period-II urine. In eight patients from whom Period-III urines were obtained only one excreted XA. This patient had excreted a large amount of XA in Period-II and the riod-III XA excretion was markedly reduced in comparison with the Period-II excretion. Four other patients who excreted XA in Period II excreted no XA in Period III.

NMN excretion in the 17 patients in Period I ranged from 0.7 mg. to 5.9 mg. (average, 2.3 mg). Period-II excretion of NMN ranged from 1.1 to 8.8 mg. (average, 4.5 mg.). The increase in excretion of NMN in Period II over Period I, defined as the increment index, ranged from 1.1-fold to 4.8-fold.

There was 4-PA found in Period I urines of all eight patients studied. The values ranged from "less than" 0.48 mg. to 2.5 mg. (average excretion, seven patients, 0.9 mg.). The 4-PA excretion in Period-III urines ranged from 1.1 to 8.5 mg. (average 2.9 mg.). The increase in excretion of 4-PA in Period III over Period I ranged from 1.8-fold to 9.4-fold.

When the 24-hour excretions of XA, NMN, and 4-PA were studied in relation to the clinical picture of the patients, consistent trends were noted in two. These patients excreted XA in Period-II urine and also had abnormal increment indices for excretion of NMN. In neither one was 4-PA excretion measured.

Comment

Evidence for pyridoxine need in the patients studied is not consistent when the results of the three tests are compared. Thus Patient 6 in the second study, excreted 4-PA in Period-I urine, had an NMN increment index of 2.3 (normal), yet excreted a large amount of XA in Period-II urine (abnormal). This discrepancy is due possibly to the fact that each of the tests varies in its sensitivity in detecting pyridoxine need, a point which will be elaborated.

The excretion of XA occurs in the urines of pyridoxine deficient animals.[11] This abnormal metabolite is obliterated from the animal urines by the administration of pyridoxine. In the study by Adam and associates[5] of babies fed a convulsigenic pyridoxine-deficient milk mixture, XA was excreted by two babies who had convulsions. After pyridoxine ingestion no urinary XA was found and the convulsions ceased. In this same study nine infants were observed who had no convulsions and XA in an unspecified amount was found in the urine of two of these babies. One of these two babies was studied in detail, and XA disappeared from the urine after the oral ingestion of 0.3 mg. a day of pyridoxine. It appeared, therefore, that pyridoxine need as measured by the XA excretion test did not correlate consistently with clinical symptoms (convulsions), and that different babies required different amounts of pyridoxine to obliterate XA from the urine.

In the present study there were eight infants and children whose XA excretion following a standard tryptophan load was studied before and after parenteral pyridoxine (three-period test). Of these eight patients five aged 11 months to 42 months excreted XA in Period II. Four of these infants had no XA in Period III, and the fifth child showed a marked reduction of excretion of XA in Period III when compared with Period-II excretion. From these data it would seem fair to conclude that the appearance of XA in the urine of children less than 4 years of age following

a DL-tryptophan load of 0.54 gm/kg. indicates a need for pyridoxine. An additional 7 infants studied by the two-period test excreted XA in Period II, yielding a total of 12 infants who excreted XA in Period-II urines. If one accepts the conclusion that the appearance of XA in Period-II urine is an indication of pyridoxine need, then 12 of the 17 infants studied gave evidence of pyridoxine need. Clinically three of these patients had hypochromic, microcytic anemia; three, febrile convulsions, and six, acute infectious illnesses of varying severity.

NMN is excreted in the urine of normal as well as pyridoxine-deficient humans. In the study of Snyderman and co-workers[1] both infants excreted this nicotinic acid derivative for long periods after pyridoxine was withheld from the diet. However, as early as 17 days after the cessation of pyridoxine intake, one baby ceased showing an increase in excretion of NMN following parenteral L-tryptophan. This test seemed to be a sensitive index of pyridoxine need. Approximately 28 days after the resumption of pyridoxine intake a normal NMN increment index was found (1.2). Apparently normal infants and adults studied by Perlzweig and associates[6] were able to increase their NMN excretion from 1.2-fold to 6-fold after ingestion of a tryptophan dose when compared with the NMN excretion without tryptophan. On the basis of urinary NMN increments of 1.2 or greater following a standard DL-tryptophan load of 0.54 gm/kg. being normal and values less than this indicating pyridoxine need, two of the patients in our study had such a need. One child (Patient 10) with anemia and convulsions had an increment index of 1.1 and Patient 7, a child with meningitis and septicemia, had a negative index (−2.7). Both patients had further indications of pyridoxine need in that both excreted XA in Period-II urines.

An additional finding of Perlzweig and associates[6] is pertinent to the interpretation of the negative increment index in Patient 7. If NMN is given to adults by mouth, only 20% to 25% of the ingested NMN is accountable as nicotinic acid derivatives in the urine. It appears as if the human can "destroy" NMN. Thus a low NMN increment index can mean failure to convert tryptophan to NMN and excretion of it or "destruction" of NMN which has been normally formed.

4-PA is the main metabolic product excreted after oral or parenteral intake of pyridoxine.[13] In the studies of Snyderman and co-workers[1] 4-PA disappeared from the urine immediately upon cessation of pyridoxine ingestion in one baby, but not until 40 days after pyridoxine withdrawal in the second baby. In the present study of eight patients whose 4-PA excretion was measured, all excreted 4-PA and thus none gave evidence of pyridoxine depletion by this test. All patients excreted an increased amount of 4-PA following pyridoxine parenterally. The patient whose increment in excretion between Period-I and Period-III urines was lowest, Patient 13, (1.8) had adequate ability to excrete NMN (increment index, 2.9) but by excreting XA in Period-II urine gave evidence of pyridoxine need by this test. On the other hand, Patient 6 with high excretion of XA in Period-II urine (48 mg.) which was lowered by parenteral pyridoxine (Period-III urine, 8.2 mg.) had a large increment in 4-PA excretion between Period I and Period III (9.9-fold). It thus appears that no definite conclusion can be drawn about pyridoxine need of humans from measuring the increments of 4-PA excretion after parenteral pyridoxine in doses of 25 mg. a day for two days.

No attempt was made to determine whether or not pyridoxine would alleviate the symptoms in patients with anemia or convulsions. Treatment of these patients consisted of blood transfusions and chemotherapy where indicated, improved diet plus vitamin supplements (including pyridoxine hydrochloride, 0.2 mg. a day), and later oral iron. Patients with convulsions were

controlled with oral or parenteral barbiturates during the acute illness. Later barbiturates were discontinued, and the convulsions did not recur up to four months after the study was initiated. It is, therefore, impossible to state what, if any, relation existed between pyridoxine need and the clinical symptoms of hypochromic anemia or convulsions.

In conclusion pyridoxine need was clearly indicated by the three period XA excretion test following a DL-tryptophan load of 0.54 gm/kg. both before and after parenteral pyridoxine in five of eight patients. There were seven additional patients who had two-period studies for XA excretion, and who excreted XA following the ingestion of 0.54 gm/kg. of DL-tryptophan. If the excretion of XA in Period-II urine under these conditions is accepted as evidence of pyridoxine need, then a total of 12 children of 17 studied had evidence of pyridoxine need. Two of these patients had further evidence of pyridoxine need by failure to show a normal increment in NMN excretion following the tryptophan load.

Clinically, of the five patients with positive three-period XA excretion tests one had severe hypochromic, microcytic anemia, one had convulsions accompanying fever and pyelonephritis, and three had acute febrile illnesses of varying severity. Of the seven patients with positive two-period XA excretion tests two had anemia, two had convulsions with fever, and three had acute febrile illnesses of varying severity. The two patients showing evidence of pyridoxine need by the NMN excretion test and the two-period XA excretion test had anemia and meningitis with septicemia, respectively. Eight patients in whom 4-PA excretions were measured had no evidence of pyridoxine depletion by this test. Five of these eight patients showed evidence of pyridoxine need by a positive XA excretion and none, by the NMN excretion test. Of the patients without evidence of pyridoxine need one had hypochromic, microcytic anemia, one had convulsions and mental retardation, and three had acute gastroenteritis with varying degrees of dehydration.

Summary

Seventeen boys under the age of 4 years were studied for evidence of pyridoxine need. Three tests were used. These included the measurement of the excretion of xanthurenic acid and N^1-methylinicotinamide before and after a standard DL-tryptophan load of 0.54 gm/kg. and the measurement of the excretion of 4-pyridoxic acid and xanthurenic acid before and after parenteral pyridoxine plus the standard DL-tryptophan load.

Patients were divided into three clinical groups. Four children had hypochromic, microcytic anemia; four children had convulsions; and nine children had miscellaneous acute infectious illnesses.

Five patients showed evidence of pyridoxine need on the basis of the three-period xanthurenic acid excretion test and seven patients on the basis of the two-period xanthurenic acid excretion test. Two of the latter seven patients showed evidence of pyridoxine need on the basis of the N^1-methylnicotinamide excretion test. No patients showed evidence of pyridoxine depletion on the basis of the 4-pyridoxic acid excretion test.

There was no consistent correlation between laboratory assessment of pyridoxine need and clinical symptoms.

Evidence for pyridoxine need was not consistent when the results of each test were compared in one patient. On the basis of data presented in this study plus data derived from the literature, it is suggested that the tests may indicate pyridoxine need in the following order of decreasing sensitivity: xanthurenic acid excretion test, N^1-methylnicotinamide excretion test, and 4-pyridoxic acid excretion test.

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"Periodic Peritonitis"

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American pediatric literature and textbooks do not contain any reports of periodic peritonitis, a syndrome which is familiar to internists in this country as well as physicians in the Near East and North Africa. This disease, often familial, apparently is limited principally to Arabs, Armenians, and Jews, but other peoples occasionally are affected.

Periodic peritonitis is characterized by abdominal pain and tenderness, fever, polymorphonuclear leucocytosis, and, at times, pain in the thorax and joints. The duration of an attack is 24 to 72 hours; it is followed by complete remission, but exacerbations occur at regular intervals. The recurrences at times may be irregular, and the remissions may become shorter with age. Most of the patients have undergone appendectomy in childhood.

There is no appreciable effect on the general health or growth or development of afflicted children. In more than half of the reported cases the onset took place in childhood, and the condition has been reported in the United States, Lebanon, and North Africa.

We recently encountered a 6-year-old boy who had periodic peritonitis, and we were able in retrospect to diagnose the disease in a second patient seen at the Mayo Clinic in 1941.*

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Read at the meeting of the Northwest Pediatric Society, Bayport, Minn., Sept. 23, 1955.

Fellow in Pediatrics, Mayo Foundation (Dr. Sturtz) and Section of Pediatrics, Mayo Clinic and Mayo Foundation (Dr. Burke).

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Report of Cases

CASE 1.—A 6-year-old boy of Armenian extraction registered at the Clinic on May 16, 1955, complaining chiefly of recurrent thoracic and abdominal pain. Eighteen months previously recurrent pain had begun. The pain usually started in the right axilla and gradually became severer; it was sharp and stabbing and seemed to "come and go." As the intensity of the pain increased, the pain moved downward over the chest to the right upper quadrant of the abdomen and it also extended through to the back. The pain was not severe enough to prevent sleeping. During the attacks the boy walked in a stooped manner. Occasionally, the pain started in the left axilla and moved downward into the left upper abdominal quadrant. There was no nausea, vomiting, or diarrhea with the attacks. As the pain became more intense the temperature gradually increased

* As the proofs of this paper were received, we observed an 11-year-old Jewish girl with periodic peritonitis. The mother said she "had spent hundreds of dollars and nine years of constant running to doctors and hospitals in an attempt to diagnose my daughter's ailment." Eight hospitalizations in a large children's hospital had failed to reveal the diagnosis. This child's paroxysms occurred every seven days and were characterized by colicky, substernal pain followed in two hours by severe epigastric pain lasting six to eight hours. The temperature increased to 103 F. The pain then gradually disappeared. Severe nausea, unaccompanied by vomiting, was present throughout each attack. Occasionally, pain in the shoulder heralded the onset of a paroxysm.

The maternal grandfather had had "sticking pains in the chest" that lasted 24 hours and recurred every 2 to 3 weeks; the pain was severe enough to necessitate rest in bed. He had had these episodes of periodic pain for more than 30 years, and "was treated many times for pleurisy." This history is strongly suggestive that this man had had periodic peritonitis, featured predominantly by stethalgia.

A typical, although mild, attack was observed in the child. The chronic, recurrent nature of the disease and the lack of effective therapy were discussed with the parents.

to about 102 F. The boy would not allow his parents to touch his abdomen during an attack. These paroxysms of pain and fever lasted two to three days, and originally recurred every 21 to 28 days. At the time of registration the paroxysms were recurring regularly every 14 days.

Twelve months before registration of the patient, results of routine blood counts, urinalysis, and an excretory urogram had been reported to be normal.

Nine months before registration an exploratory laparotomy had been done between attacks. The appendix had been removed, although grossly it appeared to be normal. The surgeon had observed no gross abdominal pathologic process. Shortly after operation infection of the urinary tract caused by a hemolytic type of Staphylococcus aureus had developed on three occasions; each infection had been successfully treated with antibiotic agents.

Family history revealed that both parents were of Armenian extraction. The father's brother had had attacks of fever yearly since his participation in a desert campaign while he was in military service. The paroxysms were accompanied by chills. His illness had been attributed to malaria, and he took quinine when he was affected.

Results of physical examination were entirely within normal limits.

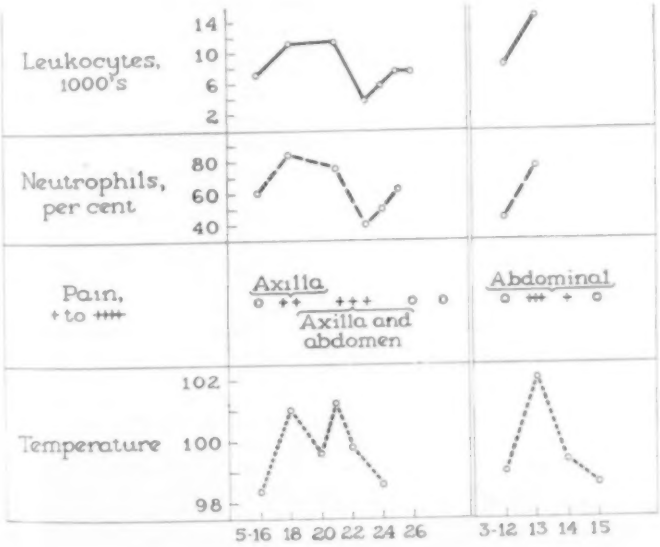
Three uninalyses disclosed no abnormalities; tests of the urine for porphobilinogen and uroporphyrin gave negative results, as did those of Coombs' test and a clot test for lupus erythematosus. Roentgenograms of the thorax and abdomen disclosed no abnormality. Culture of specimens of the blood and urine taken during an attack gave negative results, and agglutination tests for Salmonella typhosa (H), S. typhosa (O), S. paratyphi (para A), S. schottmülleri (para B), Brucella organisms, Pasteurella tularensis, and Proteus OX-19 all produced negative results. Sternal aspiration of bone marrow, done during an attack, showed no abnormality.

A typical attack was observed. The usual pain in the right axillary region developed and moved downward to the right upper quadrant of the abdomen; it was accompanied by a temperature of 101.2 F and a leucocytosis in which the count was 11,000, eighty-five per cent being polymorphonuclear neutrophiles. The attack subsided in four days without treatment (Figure).

The disease was discussed with the parents and the boy was discharged on May 27, 1955.

Comment on Case 1.—This boy had combined thoracic and abdominal pain. Reimann [8] noted a similar combination of pains in 12 of 38 patients. He also observed three patients in whom "periodic abdominalgia was preceded by several years of recurrent stethalgia."

Knowledge of this syndrome may allow the physician to recognize the fact that a patient is having an attack, since the pain and abdominal tenderness usually subside within 72 hours. However, exploratory laparotomy may be necessary in some cases, if localizing signs develop, to rule out concomitant acute surgical disease.



Laboratory and physical findings of a typical paroxysm such as occurred in both patients concerned in this report. The first patient was a boy 6 years old; the second was a boy 11 years old.

CASE 2.—An 11-year-old boy of Syrian extraction registered at the Clinic on March 11, 1941, complaining chiefly of recurrent fever and abdominal pain of 8 years' duration. At the age of 3 years paraumbilical pain, diarrhea, and a temperature of 102 F had developed. This attack subsided within 24 to 36 hours. Similar episodes occurred every one to three months for the next three years.

At the age of 6 years the condition of this patient had been evaluated in the pediatric hospital of an eastern university. Results of routine blood counts and of urinalysis were normal. A Kahn test of the serum disclosed nothing abnormal; no ova or parasites were found in the stools. Shigella dysenteriae (Flexner), S. sonnei, Salmonella aertrycke, Brucella melitensis, or Brucella abortus could not be agglutinated. Organisms of the typhoid group were agglutinated only weakly. Roentgenograms of the thorax and skull showed no abnormality, nor did an excretory urogram. Roentgenograms of the gall bladder showed it to be normally functioning, without stones. Roentgenograms of the esophagus, stomach, and duodenum showed them to be normal. Roentgenograms of the small intestine disclosed questionable early ileitis; a second examination did not corroborate this diagnosis. The patient was dismissed without a diagnosis.

The boy's paroxysms of pain and fever continued; they began to occur more frequently, and the pain extended through to the back.

When the patient was 9 years of age the attacks were appearing every 5 to 7 days. Exploratory laparotomy was performed; appendectomy was also accomplished. The liver, gall bladder, and right kidney were normal; the left kidney and spleen could not be felt. The appendix was diffusely congested and swollen; the pathologic diagnosis was chronic appendicitis. There were some enlarged nodes in the mesentery of the terminal part of the ileum. One node was removed and examined microscopically; it was found to be involved by a nonspecific inflammatory process.

When the patient was 11 years old he was examined at the Clinic. His attacks were then occurring irregularly every two to eight days, and they were featured by aching abdominal pain as well as pain in the left side of the thorax, around the scapula. Occasionally, the thoracic pain would extend to the right scapula. The temperature gradually increased over two or three days and reached a maximum of 103 F. Between attacks the patient was in excellent health.

He was 55 in. tall and weighed 73 lb. Nothing abnormal was found on physical examination.

On March 13, 1941, an attack started. The temperature increased to 102 F; the pulse was 144 beats per minute, and respirations were 32 per minute. Abdominal pain was severest in the right upper quadrant. There was considerable abdominal rigidity, and diffuse rebound tenderness was present. The attack completely subsided by March 15 (Figure).

This patient was observed over a period of several months. Many specimens of urine were examined and were found to be uniformly normal, although Streptococcus faecalis was cultured from the urine on several occasions. The value for urea was 8 mg. per 100 cc. of blood. An excretory urogram disclosed no abnormality, nor did roentgenograms of the thorax, spinal column, skull, colon, gall bladder, and small intestine. Cystoscopy was done; no abnormalities were noted. Both ureters were catheterized. Gram staining of specimens of urine from each ureter revealed an occasional Gram-negative coccic organism. The dynamics and chemistry of the cerebrospinal fluid were normal. Results of tuberculin and Trichinella skin tests were negative as were those of agglutination tests for brucellosis. Examination of the ears, nose, and throat revealed no abnormality; nor did roentgenograms of the sinuses do so. Culture of specimens of blood produced no organisms.

A course of emetine was given in April, 1941; this had no effect on the attacks. On July 4, 1941, exploratory laparotomy was done. The peritoneum showed "a considerable degree of inflammation characterized by thickening of the parietal peritoneum, redness, and petechial hemorrhages. There was likewise an inflammation of the visceral peritoneum with fibrous adhesions between the dome of the spleen and the parietal peritoneum and with redness and inflammation of the peritoneum over the gall bladder. The wall of the gall bladder was thickened; there was some redness of the small intestine." The small and large intestines, liver, common bile duct, and kidneys were normal. A specimen of muscle from the abdominal wall was taken for biopsy: it was normal.

The boy's attacks continued over the years. At the age of 13 years and again at the age of 18 years roentgenograms of the gall bladder revealed a normally functioning gall bladder without stones.

At the age of 19 years this patient again was examined at the Clinic. The attacks at this time were recurring every seven days, and they lasted three days. The abdominal pain centered around the navel and gradually shifted to the left upper abdominal quadrant. When the pain shifted to the right upper quadrant, the patient knew from experience that the attack was subsiding.

Results of urinalysis at this time were negative; culture of a specimen of urine produced no organisms. Tests for uroporphyrin and urinary porphobilinogen gave negative results, as did the tuberculin skin test and a Kline test. Roentgeno-

grams of the thorax and the thoracic part of the spinal column disclosed nothing abnormal. A roentgenogram of the gall bladder revealed normal function; no stones were present.

At the time of this report the patient was 25 years old and continued to have attacks.

Comment

Siegal[1] described five cases of periodic peritonitis in 1945. He added six cases in 1949.[2] All his patients were Jews or Armenians. He felt that the disease is closely related to allergy, since two of his patients were "atopic" and four had a family history of allergy. However, no food allergens were demonstrated; epinephrine and antihistamines failed to control the attacks.

The cause of this syndrome is unknown. Other authors have not found a relationship to allergy. No infectious agent has been implicated. The possibility of a neurologic background has been explored.[1] However, patients with abdominal epilepsy do not have abdominal physical signs or fever, and their attacks usually are controlled by anticonvulsant medication.*

Reimann has written extensively about this disorder. He has classed it in a group of recurrent diseases which he calls "periodic disease."† He includes periodic peritonitis, cyclic neutropenia, periodic fever, anaphylactoid purpura, intermittent arthralgia, cyclic vomiting, and angioneurotic edema. He has suggested that all these diseases may have a common etiologic basis. There is little supporting evidence that this is true. At present it can be said that each of these diseases is recurrent in a given patient, but that it is only the rhythmicity of the individual condition which binds them together. Periodic peritonitis seems to be set apart from the over-all group called "periodic disease" by the fact that it occurs in Armenians, Jews, and Arabs. This ethnic distribution is strikingly lacking in the other periodic diseases.

The pathologic aspects of periodic peritonitis have not been studied extensively. Reimann[8] observed pathologic changes in the appendices and gall bladders of seven patients. He noted "a sterile, mild, nonsuppurative inflammatory process involving the walls of the appendix and gall bladder in patients operated on during and between episodes." Two of his patients underwent appendectomy between episodes; the appendices of both patients were grossly normal but, microscopically, revealed some minimal changes. The patient in our Case 1 was operated upon between attacks. His abdominal organs and peritoneum were grossly normal; unfortunately, we do not have any tissue for microscopic examination. Brick[9] found acute peritonitis "of undetermined etiology" localized to the peritoneum in the vicinity of the liver in a patient operated upon during an attack. Our second patient, who was operated upon during an episode of abdominal pain and fever, had peritonitis grossly. The reaction was severest around the spleen and gall bladder.

It appears that patients operated upon during an attack often have acute peritonitis (and sometimes superimposed chronic peritonitis), while those who are operated upon during remission may have chronic peritonitis or no peritoneal abnormality at all.

Many cases of the disease have been reported from North Africa. In most of these cases the condition afflicted Jews. Benhamou, Albou, and Griguer[10] emphasized the pain in the thorax which often accompanies a paroxysm; this was a prominent feature in our first case. They noted mild splenomegaly in many of their patients. Periarteritis nodosa proved by biopsy developed in one of their patients. Mamou and Cattan[11] noted the relationship of periodic peritonitis and renal disease. Among 14 patients with periodic peritonitis, chronic nephritis developed in 8. Several of these patients were members of one family, and one man had been deaf since the age of 12 years.

Antimalarial and antibiotic agents, emetine, cortisone, and *p*-aminobenzoic acid all have been used in the treatment of periodic

* References 3 and 4.

† References 5-7.

peritonitis. None has been more than transiently effective.‡

Summary

Two cases in which periodic peritonitis occurred in children are reported. This disease is characterized by recurrent bouts of abdominal pain, abdominal tenderness, fever and leucocytosis, and, often, rebound tenderness. It often occurs in families. In most reported cases the disease has afflicted Armenians, Jews, and Arabs. The paroxysms recur over many years, and are unaffected by any treatment.

These two cases appear to be the first reported in the American pediatric literature.

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Retrolental Fibroplasia

Cooperative Study of Retrolental Fibroplasia and the Use of Oxygen

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The following is the summary from the paper "Retrolental Fibroplasia Cooperative Study of Retrolental Fibroplasia and the Use of Oxygen," appearing in the current issue of A. M. A. Archives of Ophthalmology. *Because of the tremendous interest in this subject in both fields it was felt desirable to publish the complete paper in* Archives of Ophthalmology *with a summary in the* JOURNAL OF DISEASES OF CHILDREN. *Those readers interested in the details of the investigative work are referred to the* Archives of Ophthalmology *for the complete paper.*

ROBERT B. LAWSON, M.D.

Summary

The chief purposes of the Cooperative Study of Retrolental Fibroplasia (RLF) were to determine, by means of a controlled clinical trial, whether the incidence of RLF was positively associated with the length of exposure of the premature infant to oxygen and whether restricting oxygen to that amount deemed necessary to prevent anoxia would influence the survival rate.

The study was designed so that two groups of premature infants received widely different amounts of oxygen while all other factors associated with the care of the infants were kept as similar as possible.

There were 786 premature infants in the study. These infants represent all those who were born in or brought to the 18 cooperative hospital nurseries during the study year, who weighed 1500 gm. or less at birth, and who survived 48 hours, at which time they were admitted to the study. Of these infants, 586 were followed for a minimum of two and one-half months and represent the study population so far as RLF is concerned.

One-third of the infants in each hospital who were admitted to the study during the first three months were assigned at random to a group which was to be given oxygen for 28 days (routine-oxygen group), and two-thirds were assigned to a group which was to be given oxygen only at the discretion of the pediatrician, on the basis of clinical need (curtailed-oxygen group). The assignments were made in matched sets of three infants. For the remaining nine months of the study all of the infants were assigned to the latter group. There were 53 infants in the routine-oxygen group and 533 infants in the curtailed-oxygen group who were followed sufficiently long to permit a diagnosis. Eye examinations were made at frequent intervals, in most instances until the infant was 6 months of age.

The mortality rates in the routine- and curtailed-oxygen groups did not differ significantly, either during the first three months of the study or throughout the entire year.

The incidence of active stages of RLF in the routine-oxygen group was approximately twice that in the curtailed-oxygen group ($P<0.01$). *The incidence of cicatricial grades* of the disease in the routine-oxygen group was approximately three and a half times that in the curtailed-oxygen group ($P<<0.01$).

The incidence of both active and cicatricial forms of RLF was less for infants of *single birth* than for those of *multiple birth*. The incidence of the cicatricial form of the disease for infants of single birth was only approximately one third of that for infants of multiple birth ($P<0.01$), despite the fact that infants of single birth received oxygen for two days more, on the average, and had

an average gestational age two weeks less than the infants of multiple birth.

The incidence of cicatricial grades of RLF in infants of both single and multiple birth who were in the routine-oxygen group, and whose *health status* therefore can be considered representative of all the infants in the study (classified as the "well" infant group), was approximately twice that for infants who received similarly long stays in oxygen given on the basis of clinical need (classified as the "sick" infant group).

The incidence of both active and cicatricial RLF increased rapidly with increased *duration of exposure to oxygen* for infants of both single and multiple birth. The incidence in infants of single birth increased most rapidly for exposures to oxygen of only *one or two* days. For infants of multiple birth the incidence increased up to periods of exposure to oxygen of about two weeks.

The incidence of cicatricial RLF for the most part was not dependent on the *concentration of oxygen* administered. Thus, the incidence was not appreciably greater for those infants of single birth who received an average concentration of oxygen of about 33% than for those infants who received an average concentration of oxygen of approximately 50% for similar periods of time. The incidence of cicatricial RLF for infants of multiple birth who received oxygen for relatively short periods of time (two days) likewise was not appreciably influenced by concentration. However, with longer exposures (12 days) it did increase with the average concentration of oxygen administered.

The incidence of cicatricial RLF was not appreciably dependent upon *gestational age* for infants of single birth. The effect of gestational age on the incidence of the disease for infants of multiple birth could not be determined because of variations in duration of exposure to, and concentration of, oxygen, as well as because of differences in birth weight of the infants.

The incidence of cicatricial RLF was inversely related to *birth weight* for all infants.

The incidence of cicatricial RLF was not apparently influenced by ***race, sex, type of incubator used, or any of a number of other miscellaneous factors*** associated with either the infant or the mother.

The incidence of cicatricial RLF in the group of infants who received no added oxygen after entry into the study (age 48 hours) was less than 1% (1/112). The one infant who developed the disease (Grade A, A) was known to have received 11 hours of oxygen prior to admission to the study.

Exposure to added oxygen (prior to admission to the study) for less than a total of 48 hours was accompanied by some risk of cicatricial RLF (1 infant of 52). However, the disease does not progress to the cicatricial grades as frequently as for longer exposures. Moreover the incidence of active RLF is also reduced (ca. 10%).

The severity of cicatricial RLF was not dependent upon the duration in or concentration of oxygen, gestational age, birth weight, race, sex, or geographical location of the hospital nursery for infants of either single or multiple birth.

Spontaneous regression of RLF from active Stages 1 and 2 occurred in approximately 90% of the cases of infants of single birth. Regression was much less frequent from active Stages 3, 4, and 5 for infants of single birth and a relatively rare occurrence in infants of multiple birth from Stage 2 or greater.

The age of the infant at onset of RLF was not dependent upon the *gestational age or birth weight*, but it increased with the length of stay in oxygen, particularly for longer periods (several weeks or more). Some infants developed the disease while still in oxygen.

The *average weight gain* of infants did not differ widely between groups of infants who did and did not develop cicatricial RLF.

Other factors such as number of *transfusions and infusions, frequency of medica-*

tion, dietary adjuncts, complications of pregnancy, and age of mother did not appear to affect the incidence of the cicatricial form of the disease.

Conclusions

Of the factors considered, this controlled study shows conclusively that the length of time the premature infant is kept in an oxygen-enriched environment is the important factor in the production of RLF.

Limiting the duration in oxygen to that deemed necessary to meet frank clinical emergency was shown to be without effect on the survival rate of the premature infant.

For all practical purposes there is no concentration of oxygen in excess of that in air that is not associated with risk of developing RLF.

Infants of multiple birth appear to be significantly more susceptible to RLF than infants of single birth.

Rate of withdrawal from oxygen does not appear to play a primary role in the pathogenesis of RLF.

Recommendations

The length of time a premature infant, particularly an infant of multiple birth, is kept in an environment containing oxygen in concentrations in excess of that of air should be kept to an absolute minimum, consistent with the clinical indications of anoxia. When oxygen therapy is clearly required, it should be prescribed on an hourly basis and the concentration should be as low as possible.

Case Reports

CONGENITAL ABSENCE OR ATRESIA OF A MAIN BRANCH OF THE PULMONARY ARTERY

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THE CLINICAL diagnosis of congenital absence of a main branch of the pulmonary artery was first described by Madoff and associates[1] in 1952. They found, however, that 9 cases had been recorded previously in which the diagnosis had been made at autopsy or operation. Since that time, only 23 additional patients have been reported,* bringing the total number of documented cases to 32. This figure does not include nine cases which have been mentioned in the literature but not reported.† We wish to report observations recently made in two patients with a functionally absent left pulmonary artery associated with tetralogy of Fallot.

Report of Cases

CASE 1.—An 18-month-old Mexican boy entered the U.C.L.A. Medical Center on Jan. 12, 1956. He had apparently been well until 4 months of age when the parents first noted cyanosis while crying. During the remainder of the first year, cyanosis was visible only on exertion, but thereafter was discernible even while the child was at rest. With the minimal exertion of crawling or trying to stand, he became extremely dyspneic.

Physical Examination.—Examination revealed a thin child who was 82 cm. tall and weighed 10.1 kg. There was generalized cyanosis which was most prominent about the lips and nailbeds. The blood pressure in the right arm was 126/98, in the right leg 140/110, in the left arm 126/96, and in the left leg 146/104. A Grade III systolic murmur was audible over the entire precordium, with the point of maximum intensity to the left of the sternum at the third and fourth intercostal spaces. A systolic thrill was palpable in the same area and also at the base of the heart. The second pulmonic sound was audible but of diminished intensity.

Laboratory Data.—The erythrocytes numbered 7,400,000/cu. mm., with 18.6 gm. of hemoglobin. The electrocardiogram showed right axis deviation and right ventricular preponderance. Teleroentgenograms revealed a prominent right atrium but no gross cardiomegaly, a concave pulmonary artery segment, and relatively avascular lung fields (Fig. 1). Angiocardiography was performed after the injection of 10 cc. of 70% sodium acetrizoate (Urokon) into the right median basilic vein. Films were obtained in the postero-anterior and lateral positions simultaneously, 17 frames being made in each plane over a period of five seconds. It was observed that the initial injection filled the right atrium and passed into the right ventricle, then through the rather small infundibulum into a very small infundibular chamber. At the same time as the right pulmonary artery was filling, the aorta could be visualized in its proximal portion. It was also noted that the left pulmonary artery did not fill (Fig. 2).

Fig. 1 (Case 1).—Teleroentgenogram showing a concave artery segment and relative avascularity of both lung fields.

Course.—Clinical observations and laboratory

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* References 1-10.

† References 3 and 11.

studies indicated that the diagnosis was a tetralogy of Fallot with a functionally absent left pulmonary artery. Because of the increased hazards of

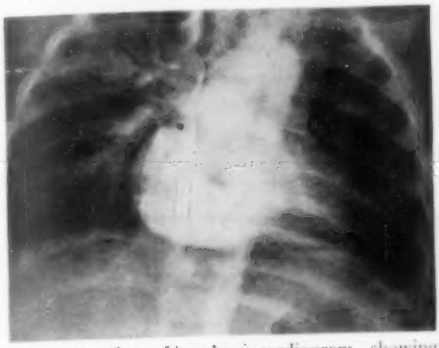

Fig. 2 (Case 1).—Angiocardiogram showing opacification of the right pulmonary artery and the aorta but no filling of the left pulmonary artery.

a Blalock procedure in the presence of a unilateral pulmonary artery, surgical intervention was not deemed advisable. The patient was discharged and is at present being followed in the outpatient department.

CASE 2.—A 6-year-old Negro boy entered the U.C.L.A. Medical Center on Jan. 7, 1956. He had apparently been well until 3 years of age when it was discovered that he had sickle-cell anemia. Exercise tolerance had been markedly impaired since that time, but no episodes of cyanosis had been observed. At the age of 5 years, he was studied at another hospital, and, in addition to the sickle-cell disease, a diagnosis of probable tetralogy of Fallot was made. This was based in part upon data obtained by right heart catheterization.‡

Physical Examination.—Examination revealed a very thin child who weighed 20.7 kg. and was 129 cm. tall. The respirations were 12 a minute, the pulse rate 96 a minute, and the temperature 37.4 C. He did not appear to be in distress while at rest. The blood pressure was 100/70 in the right arm and 140/90 in the left leg. The peripheral pulses were strong and equal. The apex beat of the heart was very forceful with the point of maximum intensity in the fifth intercostal space at the left anterior axillary line. A pronounced thrill was palpable in the third intercostal space to the left of the sternum and also at the apex. A Grade IV systolic murmur and a Grade II diastolic murmur were heard in the third intercostal space to the left of the sternal border. The second pulmonic sound was not audible. There was no hepatomegaly or splenomegaly.

‡ Cardiac catheterization data obtained through the courtesy of Dr. Paul R. Lurie, University of Indiana, Indianapolis.

Laboratory Data.—The erythrocytes numbered 3,015,000/cu. mm., with 10.5 gm. of hemoglobin. The hematocrit was 34%. The electrocardiogram showed right axis deviation with right ventricular preponderance. Teleroentgenograms revealed moderate cardiomegaly, some accentuation of the vascular markings, and a possible accessory aortic

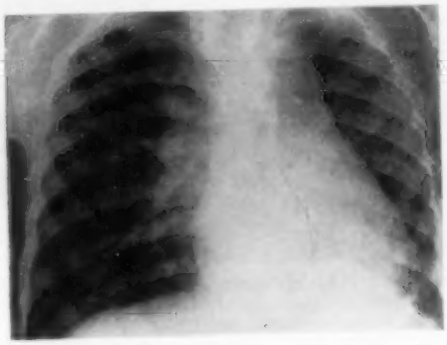

Fig. 3 (Case 2).—Teleroentgenogram showing moderate cardiomegaly and slight accentuation of the vascular markings. The latter appear to be more marked on the right than on the left.

arch or a right-sided descending aorta (Fig. 3). Angiocardiographic studies were performed after the injection of 20 cc. of 70% sodium acetrizoate in the antecubital vein. Films were obtained simultaneously in the posteroanterior and lateral positions, 18 frames being taken in each plane over a period of 7 seconds. The right atrium and right ventricle appeared to be enlarged and the lumen of the right ventricular outflow tract was irregular. Some thickening of the pulmonary valves was noted and a moderate poststenotic dilatation of the pulmonary arterial trunk was also present. The aorta was high and somewhat redundant, and the ascending and transverse portions appeared normal, but the descending portion could not be visualized. The branches of the right pulmonary artery appeared large, whereas the branches of the left pulmonary artery were rather small (Fig. 4). In retrospect, the latter probably represented an anomalous systemic supply rather than the left pulmonary artery.

Since cardiac catheterization had been performed previously, this procedure was not repeated. A report of the data obtained revealed that the pressure in the main pulmonary artery was 7/0, in the infundibulum 27/7, in the right ventricle 75/0, in the right atrium minus 1, and in the left radial artery 96/63. Oxygen concentrations were 13.2 vol.% in the main pulmonary artery, 12.1 vol.% in the right ventricle, 8.8 vol.% in the right atrium and 12.2 vol.% in the radial artery.

Course in the Hospital.—Because of the incapacitating nature of this patient's lesion, it was felt that a Blalock procedure would benefit him and, accordingly, surgery was performed on

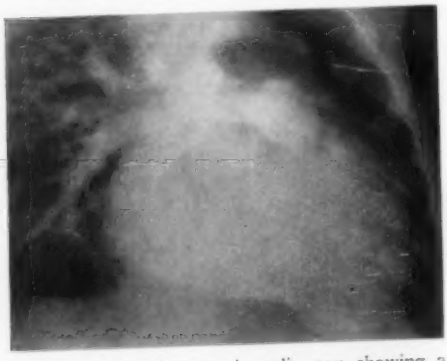

Fig. 4 (Case 2).—Angiocardiogram showing a difference in opacification of the two lung fields. This was erroneously interpreted as representing a hypoplastic left pulmonary artery. The left pulmonary artery, however, was found at autopsy to be atretic.

Jan. 12, 1956. At the time of operation, determination of the systolic pressure in the main pulmonary artery was 32 mm. of mercury. It was observed also that the left pulmonary artery was atretic for a distance of approximately 3.5 cm. from the junction of the right and left pulmonary arteries. Distal to this atretic segment, the vessel was found to have a very small lumen. Because the pressure in the main pulmonary artery was found to be adequate, the operation was terminated without performing any corrective procedure. Postoperatively, the patient developed a sickle-cell crisis and septicemia and died four days following the thoracotomy.

At autopsy, the atretic portion of the left pulmonary artery was again defined as well as the features of a tetralogy of Fallot. The presence of a vascular ring was also demonstrated, there being a persistent right and left aortic arch connected anteriorly by a vessel which was rather short but of fairly large caliber.

Comment

Absence or atresia of a main branch of the pulmonary artery is reportedly a rare condition. However, the present awareness of congenital vascular anomalies and the more widespread use of angiocardiography will probably demonstrate that it is not the extreme rarity suggested by the literature. It is commonly associated with other congenital defects of the heart or its major vessels, tetralogy of Fallot having been present in 10 of the 34 cases.§ Recognition of this association of anomalies is of more than academic interest to the surgeon who contemplates a Blalock procedure, since clamping of a unilateral pulmonary artery is extremely hazardous. In such patients, a pulmonary valvulotomy or infundibulectomy or even open cardiac surgery, with the aid of extracorporeal circulation, may be preferred.

When the pulmonary artery supplying one lung is functionally absent, certain alterations in the blood flow must necessarily occur. A brief consideration of the embryologic development of the pulmonary arteries lends to a better understanding of the altered circulation encountered under such conditions. The pulmonary vasculature develops from a ventral and a dorsal anlage which communicate with each other by way of the postbranchial pulmonary plexus. Normally, the dorsal anlage, which arises from the aortic branches, largely disappears while the ventral anlage ultimately becomes the main pulmonary artery. Should the ventral anlage fail to develop normally, then the dorsal aortic branches may persist and continue to supply the lung in postnatal life. In the embryologic development of the pulmonary vasculature then, the aortic or systemic components tend to compensate for lack of development of the pulmonary artery channels. In order for a patient with an absent pulmonary artery to survive, the lung must be supplied by the systemic circulation. This need is met either by hypertrophy of the existing systemic arteries to the lung or by the development of aberrant vessels arising from the aorta or its branches.[13]

In many patients, clinical symptoms attributable to the anomalous pulmonary blood supply are either absent or minimal. Increased vascular pressure with augmented blood flow to the affected side may result in cough, hemoptysis, decreased exercise

§ References 5, 10, and 12.

tolerance, or recurrent bouts of pneumonia. Although there are no pathognomonic physical findings, limited chest expansion with diminished breath sounds and normal resonance on the involved side may sometimes be elicited. Generally, suspicion of congenital absence of a pulmonary artery will arise from appreciation of certain features in the conventional chest roentgenogram. These features are (1) reduction in the volume of the abnormal lung, (2) absence of the normal hilar vascular shadows of the involved lung, (3) varying degrees of mediastinal herniation toward the anomalous lung, and (4) occasionally, elevation of the ipsilateral leaf of the diaphragm. Fluoroscopy may show deviation of the mediastinum toward the involved side on deep inspiration, and hilar pulsations in the anomalous lung may be absent. Angiocardiographic studies, however, are necessary to establish a definitive diagnosis. The contrast media will appear in the pulmonary vasculature of the normal lung but not in the affected side. If many films are taken in rapid succession, the arterial supply to the involved lung may be visualized after the aorta becomes opacified.

The clinical picture may, of course, be entirely dominated by the associated cardiac anomaly, and this is especially true when the malformation is tetralogy of Fallot. In this combination of anomalies the absent pulmonary artery is usually on the left side, and absence of the left hilar shadows in the conventional chest roentgenogram is often difficult to demonstrate. On angiocardiographic study, moreover, if a sizable anomalous systemic supply exists, it will opacify at the same time as the pulmonary artery because of the overriding aorta. As in Case 2 this may be misinterpreted as a hypoplastic rather than an absent pulmonary artery.

Since the blood supply to the involved lung is entirely arterial, one would expect that under normal circumstances there would be no oxygen uptake from the gas in the alveoli. Bronchospirometry in a patient studied by Madoff and associates [1] indicated that this is actually the case. In their patient there was no significant oxygen uptake in one lung and thus the total ventilation was twice normal. They calculated the "effective bronchial arterial flow" to be about 17% of the left ventricular outflow, whereas in normal persons it is approximately 1%. Pulmonary function studies have also been reported by Steinberg and associates [2] in two adult patients with congenital absence of a main branch of the pulmonary artery. They were unable to calculate the oxygen uptake in the involved lung, however, since bronchospirometry was not done.

Because of the small number of cases thus far observed, recommendations for therapy are at present only tentative. Surgical intervention will no doubt be influenced to some degree by the type of associated cardiovascular anomalies. When functional absence of a pulmonary artery is the principal defect, surgery is not indicated unless the patient is symptomatic. Chronic or recurrent pulmonary infection may be an indication for pneumonectomy. When the systemic blood flow to the anomalous lung is unusually large and results in pulmonary congestion, then rerouting, reducing, or removing the anomalous vessels should be considered.

Summary

Two patients with a functionally absent left pulmonary artery are presented. Tetralogy of Fallot was also present in both patients. The recognition and treatment of a unilateral pulmonary artery are briefly discussed.

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Abstracts from Current Literature

Acta Paediatrica Stockholm

45, Supplement (Feb.) 1956

Infantile Genetic Agranulocytosis. R. Kostmann—p. 105.

45:103-210 (March) 1956

Blood Gas Determinations on Premature Infants: Investigations of Premature Infants with Early Neonatal Dyspnea (The Hyaline Membrane Syndrome). W. Blystad.—p. 103.

Histological Findings Characteristic of Rickets in Foetuses and Young Infants. G. V. Sydow, S. Ranstrom, D. Berezin, and O. Axen.—p. 114.

Cortisone Treatment of Idiopathic Pulmonary Hemosiderosis. S. Halvorsen.—p. 139.

Effect of Fatty Acids of Human Milk and Cow's Milk on Intestinal Lactobacilli. H. Gyllenberg, M. Roesander, and P. Roine.—p. 147.

Third Generation Syphilis in an Infant with Sero-Tests Indicating Passively Transferred Maternal Reagins. A. Sundal and T. M. Vogelsang.—p. 161.

Hypothyreoid Signs in Encephalopathy. M. Avignon and R. Zetterstrom.—p. 170.

Effect of Ascorbic Acid upon the Hemolysis of Human Blood Caused by Oxygen. N. Raiha.—p. 176.

*Appearance in Children's Sera of Substances Capable of Neutralizing Canine Distemper Virus: Preliminary Report. G. Carlstrom.—p. 180.

Systemic Lupus Erythematosus in Childhood: A Clinical Study. R. Zetterstrom and G. Berglund.—p. 189.

Appearance in Children's Sera of Substances Capable of Neutralizing Canine Distemper Virus: Preliminary Report.—This paper reports on further studies relating to the finding of increasing titres of neutralizing antibodies to canine distemper virus (C. D. V.). Adams has reported an association of neutralizing antibodies to canine distemper virus and a respiratory disease in children, but whether this indicates a causal relation has not been proved. Carlstrom tested human sera for neutralizing antibodies by intracerebral inoculation of mice 24-48 hours old with mouse adapted virus-serum mixtures. Neutralizing antibodies were seldom found in serum from children under 4 years of age but began to appear between 4 and 6, so that most persons over 10 years had neutralizing antibodies. This corresponds with similar studies of Karzon in Buffalo, except for a tendency to appear somewhat later in the Swedish population.

Attempts to relate this neutralizing activity to any specific disease in hospitalized patients in Stockholm has not been successful. Further studies in children under 6 years are being carried out.

American Journal of Medicine, New York

20:317-486 (March) 1956

Ebstein's Disease. James W. Brown, Donald Heath, and William Whitaker.—p. 322.

Ventricular Septal Defect with Aortic Incompetence Simulating Patent Ductus Arteriosus. Paul Winchell and Fouad Bashour.—p. 361.

*Idiopathic Pulmonary Hemosiderosis. J. R. Browning and John D. Houghton.—p. 374.

Therapy of the Malignant Lymphomas. Charles A. Hall and Kenneth B. Olson. I. A Study of 116 Cases.—p. 392; II. A Review.—p. 399.

Idiopathic Pulmonary Hemosiderosis.—This paper describes the occurrence of idiopathic pulmonary hemosiderosis in three young men seen within a four-year period on a 150-bed medical service. Although this fact suggests that the illness occurs more frequently among young adults than has been previously recognized, it is primarily an illness of children; 30 of 33 previously reported cases have been in children. The children may have been sickly from birth; more commonly, symptoms begin in childhood and are manifested by recurrent two- to seven-day episodes of dyspnea, cyanosis, cough with hemoptysis, fever, tachycardia, and anemia of the iron deficiency type but with reticulocytosis. Findings on examination of the chest vary from unremarkable to rales, dullness, and consolidation. X-rays show a similar variability from a course generalized mottling to diffuse hemogenous opacities. The findings of hemosiderin-filled macrophages in the sputum aids in confirming the diagnosis.

The etiology is not understood; the possibilities suggested include a primary circulatory

defect, a defect in the elastic tissue of the blood vessels and lung, and primary iron storage in the lung. Pathologic studies reveal an increase in the collagen, reticulum, and muscle together with decrease or fragmentation of elastic tissue in small blood vessels and alveolar walls. There is not the marked vascular abnormality seen in hemosiderosis complicating mitral stenosis.

Therapy in the past has been symptomatic and included transfusions, oxygen, sedatives, and antibiotics. On such therapy two of the three young men here reported died within four years of the onset of their symptoms. Even though the third patient who received, in addition, steroid therapy has survived, it is felt that no conclusions should be drawn from this single observation, but that the use of ACTH or cortisone merits further trial.

The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, Springfield, Ill.

75:847-1026 (May) 1956

*Excretory Pyelography in Infants: Technique for Intravenous Injections. Edward B. Singleton and Gunyon H. Harrison.—p. 896.

*The Role of Irradiation in the Treatment of Wilms' Tumor in Children. H. Dabney Kerr and Robert E. Flynn.—p. 971.

*A simple Approach to the Roentgen Diagnosis of Abdominal Tumors in Infants and Children. Charles M. Nice Jr., Alexander R. Margulis, and Leo G. Rigler.—p. 977.

The Role of Irradiation in the Treatment of Wilms' Tumor in Children.—Twenty-eight cases seen at the University of Iowa Hospital from 1931 to 1951 are summarized. Wilms' tumor is found most frequently in the first 4 years of life. Of 14 cases treated with irradiation alone, 28.6% survived two years and 14.3% survived five years; all died of the disease. Of 14 cases treated with irradiation and nephrectomy, 50% survived two years and 35.7% survived five years. The method of treatment in these children was the use of irradiation followed by nephrectomy.

One of the cases which survived five years died later without evidence of metastatic neoplasm, but from causes directly related to irradiation of metastases. It is the authors' opinion that treatment of Wilms' tumor by irradiation followed 8 to 12 weeks later by nephrectomy is the treatment of choice. In the event of metastatic disease they believe the metastases should be handled by intensive irradiation.

The possibility of metastases after the two-year survival period is well demonstrated.

Excretory Pyelography in Infants: Technique for Intravenous Injection.—The problem of obtaining satisfactory excretory pyelograms in the young pediatric patients has always been significant. The finding of gas in the small intestine is a normal finding in this age group but one which is perplexing. Also there is considerable problem with insufficient concentration of contrast material. In the infant use of preliminary enemas are of little value and cathartics do not help to decrease the amount of gas.

In the past, several articles have mentioned the use of carbonated beverages which will distend the stomach, and the authors' report that they are using the following technique. The infant is on a scheduled feeding with the last bottle withheld approximately six to seven hours prior to the examination. A preliminary scout film of the abdomen is obtained, and then the infant is inspected for a suitable vein. The veins of the scalp, hands, wrist, or feet are the ones which are usually used. The injection is made using the technique described by Gardner and Murray in 1950 for administering intravenous fluids to infants. A short-bevel needle without the usual hub is attached to a polyethelene tube. If the vein to be used is in an extremity this extremity is attached to a splint. If a scalp vein is to be used the common pediatric method is followed. The needle is inserted into a vein and a 10-cc. syringe filled with sterile saline or water is used to make a preliminary injection. If no wheal appears, and it is certain that extravasation is not occurring the contrast material to be used is injected.

As soon as the injection is begun, the infant is given a bottle containing a sweet carbonated beverage, and films are obtained at 5, 10, 15, and 30 minutes. The carbonated drink serves to distend the stomach, and the kidneys can be visualized through the air-filled stomach. With this method the authors' report successful pyelograms in more than 200 consecutive infants.

A Simple Approach to the Roentgen Diagnosis of Abdominal Tumors in Infants and Children.—This paper presents a description of an approach to the diagnosis of abdominal masses in infants and children with special emphasis on radiographic diagnosis.

The basic approach is an attempt to determine whether the mass is intraperitoneal or extraperitoneal. If intraperitoneal an attempt is made to determine whether it is intimately connected with the liver or spleen. The topographic classification used is as follows:

I. Intraperitoneal masses
   1. Masses in the region of the liver and spleen
   2. Other intraperitoneal masses

II. Extraperitoneal masses
   1. Masses of the renal and adrenal regions and other extraperitoneal masses.

The article concerns itself with the relationship of various masses to the adjacent structures. The displacement of kidney, stomach, and duodenum by a mass in either the right or left lobe of the liver is discussed on a relational basis. This is correlated with the various masses which may occur within the liver.

The choledochal cyst is seen as a mass in the right upper quadrant in a jaundiced infant and forms a characteristic impression on the posterolateral aspect of the second portion of the duodenum. Enlargement of the spleen is discussed, and encroachment upon the stomach by the enlarged spleen is demonstrated.

Other intraperitoneal masses, such as mesenteric and omental cysts, Meckle's diverticulum, enterogenous cyst or alimentary duplication, abscesses, intussusception, teratomas, and dermoid cysts of the ovary, and lymphangioma of the intestine, are discussed.

The masses of the renal and adrenal regions, which are retroperitoneal tumors, displace small intestinal loops in an anterior direction and displace retroperitoneal structures in the direction of their growth. The significance of anterior displacement of the duodenojejunal junction is mentioned, since it can only occur by retroperitoneal growth.

Other extraperitoneal masses, such as reptroperitoneal teratoma, pancreatic cysts and pseudocysts, lymphomas, uracal cysts, hydrometrocolpos, extraperitoneal hemangioma, and mengingoceles, are well discussed, and differential diagnosis in each of these conditions is gone into in some detail. The use of the lateral view in simple roentgenography to determine displacement of normal structures by a mass lesion is emphasized.

American Review of Tuberculosis, New York

73:609-794 (May) 1956

Growth of Mycobacterium Tuberculosis in Liquid Media. Irving L. Miller and William G. Roessler.—p. 716.
The Relationship Between the Catalase Activity, Hydrogen Peroxide Sensitivity and Isoniazid Resistance of Mycobacteria. Robert Knox, Pauline M. Meadow, and Anthony R. H. Worsham.—p. 726.
The Neutralization of Isoniazid Activity in Mycobacterium Tuberculosis by Certain Metabolites. Hilda Pope.—p. 735.
The Effect of the "Anti-Isoniazid" Substance Produced by Mycobacteria on the Chemotherapeutic Activity of Isoniazid in Vitro. Anne S. Youmans and Guy P. Youmans.—p. 764.
*Isoniazid Susceptibility, Catalase Activity and Guinea Pig Virulence of Recently Isolated Cultures of Tubercle Bacilli. Emanuel Wolinsky, Marjorie Smith, and William Steenken Jr.—p. 768.
*Purified Dihydrostreptomycin. Stephen C. F. Mahady, F. L. Armstrong, and J. Monroe.—p. 776.
A Simple Device for the Microculture in Blood of Tubercle Bacilli in Pathologic Specimens. P. Croce and N. Luridiana.—p. 785.

73:795-986 (June) 1956

The Relationship of Tuberculin Sensitivity and Adrenocortical Function in Humans. James J. Lane Jr., Edmund R. Clarke Jr., and Thomas H. Holmes.—p. 795.
The Effects of Glucose and of Oxygen on Autolysis of Mycobacterium Tuberculosis. B. U. Bowman Jr. and W. B. Redmond.—p. 907.
Human Infection with the "Yellow" Acid-Fast Bacillus. Lawrence E. Wood, Victor B. Buhler, and Ann Pollak.—p. 917.
*A Comparative Study of Laryngeal Swabs and Gastric Lavage in the Detection of Tubercle Bacilli. J. I. Tonge and P. G. Hughes.—p. 930.
*Case Report: Tuberculous Meningitis Developing in the Course of Isoniazid Therapy. Edith M. Lincoln and George I. Lythcott.—p. 940.

Isoniazid Susceptibility, Catalase Activity and Guinea Pig Virulence of Recently Isolated Cultures of Tubercle Bacilli.—From a study of 131 cultures of 74 patients treated

with isoniazid in dosage of 10 mg/kg. body weight a day, the authors reached the following conclusions: (1) the finding of a negative catalase test in a culture of tubercle bacilli is significant in that it indicates reliably a moderate to high degree of isoniazid resistance and the probability of attenuation of virulence for guinea pigs, and (2) all degrees of isoniazid resistance or susceptibility may be noted among catalase-positive strains and their virulence for guinea pigs cannot be predicted. An uncontaminated culture of acid-fast bacilli which gives a very strong catalase reaction should be suspected of being either a saprophyte or an "atypical" acid-fast strain.

Purified Dihydrostreptomycin.—An especially purified batch of dihydrostreptomycin was used in the treatment of 32 patients. Length of therapy varied from 5½ to 21 months. The incidence of ototoxic complications (approximately 25%) was the same as that reported by the same investigators in their original series. While the clinical effectiveness of the specially purified preparation seemed to be the same as that of standard forms of dihydrostreptomycin, the ototoxic property was not eliminated.

A Comparative Study of Laryngeal Swabs and Gastric Lavage in the Detection of Tubercle Bacilli.—In an effort to determine the comparative efficiency of the laryngeal swab and gastric washings in obtaining cultures of Mycobacterium tuberculosis in patients without sputum, the authors made 1305 examinations by each method in a total of 465 patients.

A single gastric lavage was found to be almost twice as effective as three laryngeal swabs in obtaining cultures positive for M. tuberculosis.

Tuberculous Meningitis Developing in the Course of Isoniazid Therapy.—The authors report a proved case of tuberculous meningitis occurring in a 3½-year-old girl of Puerto Rican extraction after 8 months of isoniazid therapy. Isoniazid dosage ranged from 3.5 to 4 mg/kg. of body weight. Insofar as could be determined, isoniazid therapy was uninterrupted.

The child has had a good but slow response to therapy with persistence of lymphocytic cells in the cerebrospinal fluid for 17 weeks after the institution of therapy.

Archiv für Kinderheilkunde, Stuttgart

151, No. 3, 1955

Editorial: Gynecomastia. Rominger.
*On the Antimycotic Treatment of Interstitial Pneumonias in Infants. Petersen.
*On Exogenous Malformations and Developmental Disturbances, Particularly Virus Embryopathies. Middendorf.
Carbohydrate Metabolism During Antibiotic Treatment. Groh.
On the Pathogenesis and Treatment of Staphylococcic Enteritis. Souchon, Huther, and Warnecke.
Contribution to the Problem of Congenital Cirrhosis of the Liver. Fincke.

152, No. 1, 1955

Editorial: Pulmonary Hyaline Membranes in the Newborn. Kloos and Wulf.
*Contribution to the Etiology and Therapy of Stuttering in Children. E. Geisler.
Constitutional Therapy, in the Age of Development. Wittneben, Santelmann and Girgensohn.
Eosinophilic Granulomatosis, It's Relations to Abt-Letterer-Siwe's Disease and Hand-Schueller-Christian's Syndrome. Santelmann and Girgensohn.
Critical Remarks Concerning Breast Milk Conservation with Streptomycin. Damerow.
Experiences with the Treatment of the Nephrotic Syndrome with Adrenocorticotropic Hormones. Salzmann.
Clinical Observations on Malignant Testicular Tumors in Infancy and Childhood. Schmid.

Contribution to the Etiology and Therapy of Stuttering in Children.—The author combines in this paper a complete and thorough analysis of the historical concepts, beginning with Kussmaul's "spastic coordination neurosis," the hereditary, postinfectious, environmental, psychoanalytic theories with personal observations at the University Children's Hospital in Würzburg. This is a city of old culture, with 83,000 inhabitants, 76% of the city destroyed by bombing, returning war prisoners, and difficult family conditions. Consequently, abundant opportunity is had to explain stuttering by psychic traumas or constant frictions.

There are observations of the author that illustrate such etiological relationships. But it is of particular interest that this study, which might easily favor the environmental factors as predominant on account of the admitted patients in hospital and outpatient department, emphasizes the constitutional etiology that accounts for the occurrence between the age of 3 and 5 years without special external causes. Of special interest are those cases that began immediately after an infectious disease and showed definite changes in the electroncephalogram.

Of the greatest importance is the treatment in the preschool age, since discouragement and over-exertion in over-crowded school classes may easily jeopardize the success.

On the Antimycotic Treatment of Interstitial Pneumonias of Infants.—The only conclusive evidence of mycotic pneumonia is the histological detection of intra-alveolar inclusion bodies, since interstitial pneumonia is secondary and nonspecific. Though the author observed 12 cases of affirmed histological diagnosis since 1952, he succeeded now for the first time in obtaining positive serological fungus antibodies. Since 1952, he has continued his efforts of specific therapy, since antibiotics proved to be unsuccessful in the treatment of the alarming dyspnea and the frequently rapid downhill course. "Kavitrat," a synthetic vitamin K product, showed satisfactory results, in spite of the danger of hemolytic anemia after high dosage and prolonged application and though it remained ineffective in combination with Aureomycin that obviously counteracted the fungus growth inhibition. The author, in his endeavor to institute some combined treatment, revived the administration of benzoic acid esters ("Nipa-Ester") that had been applied back in 1924 against mycotic pulmonary infections but faded into oblivion under the more spectacular influences of the sulfonamides. "Kavitrat" is administered by intravenous route, (20 mg. twice daily). "Ni-Nip", given orally or by polyethylene catheter with the formula or breast milk, diminishes the dreaded cyanosis without additional oxygen rather rapidly; food intake improves, and the baby, previously in utmost distress, soon begins to smile. Concomitant with the disappearance of the chest retractions, x-ray shows the subsiding of the marked diaphragmatic depression and the diffuse mottling of the pulmonary fields.

On Exogenous Malformations and Developmental Disturbances, Particularly Virus Embryopathies.—There is a discrepancy in regard to the proportional frequency of congenital anomalies supposedly due to intrauterine virus infections. The Australian statistics concerning rubeola as cause list 50% to 100%, the U. S. and British reports fluctuate between 10% and 80%, all European communications give such a low incidence that abortion appears unjustified, besides the rather unreliable history of actual German measles after conception. From the didactic standpoint, it is desirable to demarcate "Genetopathies" that may be genetic or preconceptional on a nonhereditary basis. They are responsible for syndromes of the so-called pleiotropic character and the involvement of several germ layers. Postconceptional are the "blastematoses" in incipient embryonic stages that effect the organizers, the later embryopathies after completion of the blood circulation and the inflammatory intrauterine diseases after the finished organogenesis. Though virus infections selectively affect (as in the "postrubella syndrome") the ectoderm, the completed clinical malformation often confronts the observer with complex signs that are difficult to disentangle. Nevertheless, one must try in any given case to reconstruct an entity from an etiological viewpoint. The author gives examples, particularly of malformations of the lens, where the form of the cataract (polar, nuclear,) facilitated the determination of the embryonic month where anomalies have probably occurred. This analysis is imperative from the standpoint of genetic counseling and correct interpretation, in spite of the great difficulties and the mutual interplay of genetic and postconceptional factors.

Archives of Disease in Childhood, London

30:479-558 (Dec.) 1955

Leprechaunism. Philip Rainsford Evans.—p. 479.
*Palpable Contractile Pyloric Tumours in the Newly Born. W. S. Craig.—p. 484.
Infantile Pyloric Stenosis. J. W. Gerrard, J. A. H. Waterhouse, and D. G. Maurice.—p. 493.
Infantile Hypertrophic Pyloric Stenosis in Parent and Child. Thomas McKeown and Brian MacMahon.—p. 497.
*Kernicterus and Prematurity. V. M. Crosse, T. C. Meyer, and J. W. Gerrard.—p. 501.
Hypoprothrombinaemia in the Newborn. A. S. Douglas and P. Davies.—p. 509.
Potassium Levels in Exchange Transfusion. W. A. B. Campbell.—p. 513.
Paroxysmal Tachycardia in Infancy. John Apley, Beryl D. Corner, and Thomas C. Gibson.—p. 517.
The Weight in Pink Disease. T. Colver.—p. 524.
Sudden Mental Deterioration with Convulsions in Infancy. R. S. Illingworth.—p. 529.
A Form of Lipoidosis of the Adrenal Cortex in an Infant. A. T. Sandison.—p. 538.
Mental Retardation, Pigmentation of the Skin, Xanthomatosis and Leukaemia. J. L. Emery, J. Lorber, and J. D. Sheward.—p. 542.
A Study of the Onset of Respiration in the Newborn. J. S. Fraser.—p. 546.

Palpable Contractile Pyloric Tumours in the Newly Born.—A pilot clinical study intended to investigate the significance of palpable contractile pyloric tumors in newborn babies of under 2 weeks of age is described.

Clinical material consisted of two series of cases, 21 infants in whom failure to progress was associated with recurrent vomiting or regurgitation, and 115 infants whose progress was satisfactory with no signs of symptoms of disturbed health.

Palpable contractile pyloric tumors were detected in 17 of the 21 infants in the first group and in 25 of the 115 infants in the second.

Details are given of the system of examination employed, the standards adhered to in determining the presence of a tumor, the methods of clinical management, and the results of x-ray screening.

It is suggested that in the absence of muscular hypertrophy the tumor is evidence of segmental spasm of the pyloric musculature, which is not to be regarded as necessarily evidence of abnormal function.

Instances of spontaneously subsiding recurrent vomiting (and regurgitation) in infants in whom tumors were felt are described and the suggestion made that these cases are examples of pylorospasm of a degree indicative of abnormal function.

Difficulties in the way of differentiating pylorospasm from hypertrophic pyloric stenosis in the early days of life are outlined and tentative suggestions advanced.

No rigid conclusions have been arrived at, and the purpose of the study is to focus attention on a subject which is considered to merit organized research.

Kernicterus and Prematurity.—Details have been given of the mode of onset, mortality, and signs in survivors of 60 babies developing kernicterus associated with prematurity only.

Antenatal, natal, and postnatal factors which might have contributed to the development of kernicterus in these cases have been analysed, and a comparison has been made with 60 controls and with all premature babies admitted to the units under investigation.

Bilirubin levels have been studied in 12 premature babies with kernicterus and in a series of normals.

The incidence of kernicterus and its mortality were greatest in those who were most immature at birth, as evidenced by the birth weight and period of gestation.

The postnatal bilirubinemia was also greatest in the babies who were most immature, as evidenced by the weight at birth.

In 10 of 12 babies with kernicterus bilirubin levels rose above 18 mg/100 cc. Levels of this order were uncommon in unaffected prematures, but they were encountered in six instances.

A history of anoxia and of excessive therapy with vitamin K (Synkayvite) was commoner in babies developing kernicterus than in controls, and may have contributed to the development of this complication, but the most important underlying etiological factor appeared to be the immaturity of the infant and, more particularly, the immaturity of the liver.

MISCELLANEOUS

Anatomy and Physiology

CHEMICAL EXAMINATION OF SERUM PROTEINS: PROTEIN-BOUND CARBOHYDRATES IN INFANTS AND ADULTS. HELLMUT KELLNER AND HEINRICH SUEDHOF, Monatsschr. Kinderh. 103:385-388 (Aug.) 1955.

Determinations of carbohydrates bound to serum proteins were performed on 20 healthy infants and adults. Average values were, for infants, 3.92%, for adults, 2.64%. The ratio of hexose to glucosamine was toward glucosamine in infancy. Considerable variation in the value for protein-bound carbohydrate existed in the infant group.

HARTENSTEIN, Syracuse, N. Y.

A SEDATIVE AND HYPNOTIC IN PEDIATRICS FREE FROM BARBITURATE. HANS WEBER, Med. Klin. 50:1909-1910 (Nov.) 1955.

The active constituent of "Noludar" is 2,4-Dioxo-3, 3-ethyl-5-methylpiperidin. It was used with benefit in infants with various diseases accompanied by severe states of unrest. With a dosage of 10 to 20 mg/kg., sleep was induced as a rule within 20 minutes with a duration of 2 to 3 hours. A dosage of 125 to 500 mg. was used in children 1 to 6 years old, while in the

age group from 6 to 11 years 250 to 500 mg. was given. With appropriate dosage administered one to three times during the day, a sedative effect was noted.

AMBERG, Rochester, Minn.

ELECTROLYTIC BALANCE BY VOLUME AND BY IONOGRAM IN ACUTE NUTRITIONAL DISEASES IN INFANCY. J. P. LLINAS, Arch. Pediat., Barcelona 5:461-502 (March-April) 1955.

The author has made a very detailed study of 30 children with acute nutritional diseases. In all volume determinations the method used was that of Evans Blue and the ionograms were done by the photometric system of Kipp.

All the values were studied with relation to weight of the child, the height and volume determinations.

Comparing results in the use of an absolute value and relative value by milliequivalents, the general conclusion was that when working with absolute values, the percentages of sodium chlorides, potassium, and protein have the tendency to diminish during the course of acute nutritional diseases.

No such uniformity exists when the milliequivalent system is used.

ALLEN, Santa Fe, N. Mex.

THE RELATIONSHIP OF BRAIN TISSUE PHOSPHATASE TO AGE IN THE MOUSE. WOLFGANG ALBRECHT, Monatsschr. Kinderh. 103:412-414 (Sept.) 1955.

Brain tissue of mice of various ages was examined for phosphatase activity, both in total homogenates and in extracts.

During the first few days of life alkaline phosphatase was found to be significantly higher than acid phosphatase. Alkaline phosphatase values doubled and gradually decreased thereafter, whereas acid phosphatase values remained unchanged until the 30th day of life. At this time alkaline phosphatase activity dropped below acid phosphatase. Both acid and alkaline phosphatase in adult mice were low compared with total nitrogen. Acid phosphatase was only very slightly higher than alkaline phosphatase.

HARTENSTEIN, Syracuse, N. Y.

ACETYL CHOLINE CONTENT AND ACTIVITY OF HUMAN BREAST MILK. S. HUKOVIC AND I. HADZIC, Monatsschr. Kinderh. 103:414-415 (Sept.) 1955.

Using the method of denervated blood leeches, it was demonstrated that 1 cc. of fresh human breast milk contained 0.1-0.5 gm. acetyl choline.

Isolated cat intestine in situ showed increased peristalsis and mild spasms under the influence of human breast milk.

Therefore, it was concluded that under normal conditions the number of stools of infants fed breast or cow's milk was also dependent on the acetyl choline content of the milk.

HARTENSTEIN, Syracuse, N. Y.

Biochemistry; Bacteriology and Pathology

ANTISTREPTOLYSIN REACTION IN DISEASES OF CHILDHOOD. H. KUPATZ & W. KOEHLER. Monatsschr. Kinderh. 103:415-421 (Sept.) 1955.

During the course of one year, 1255 antistreptolysin determinations were performed on 784 children with various illnesses. It was found that only serial titers and not single tests were of value in corroborating diagnostic impressions. Serologic tests, such as antistreptolysin tests, can be of value only when used in close conjunction with clinical evaluation. Anamnestic and nonspecific reactions were found frequently; the latter in leukemia and adiposogenital syndrome.

No consistently uniform upper limit of normal for antistreptolysin titers was found for children. For practical purposes two upper limits were considered sufficient: For ages 0-4 months and 6-14 years it was 250 Units. For ages 5 months-5 years, 150 Units. The main value of the test was considered to be in the differential diagnosis of rheumatic diseases; especially when paralleled by similar tests.

Another field in which antistreptolysin determinations were found to be valuable was in the search for etiological agents for various illnesses. Infections with beta hemolytic streptococci (groups A, C, and G) could be recognized by use of the test. For example, the etiology of pneumonia due to streptococci was thus elucidated.

Persistently elevated antistreptolysin titers were considered to signify relapse and only persistently normal levels were consistent with clinical cures.

HARTENSTEIN, Syracuse, N. Y.

Metabolism; Infant Feeding; Milk and Other Foods

A Metabolic Study of Two Cases of Celiac Disease, and the Effect of Farina in the Diet. by A. Jemma and M. G. Bove, Minerva Pediat. 7:610 (May 19) 1955.

Two children with celiac disease were shortly relieved of the symptoms—big abdomen, diarrhea, fatty stools, failure to gain in weight—by being put on a diet which omitted wheat flour.

Previous to being put upon this diet, one of the children had been fed a diet containing 50 gm. of farina; the child had diarrheal stools, rapidly lost in weight (370 gm. in two weeks), and the quotient of absorption of the food was 73%. When rice and potato were substituted for the farina, the general condition of the child improved, and after three weeks the child had gained 500 gm. in weight and showed a quotient of absorption of 94%.

Higgins, Boston.

Prematurity and Congenital Deformities

Importance of Anoxia in Relationship in Congenital Encephalopathies. A. Ballabriga and J. M. Samso, Arch. Pediat., Barcelona 5:511-525 (March-April) 1955.

The fact that newborn organisms can withstand more anoxia than the adult one is well known. The experiments of Reiss and Haurowitz showed the adult rat suffered permanent injury after one minute of anoxia, whereas the newborn could survive up to 44 minutes.

The authors describe their own experiments with rabbits and guinea pigs done under careful aseptic surgical conditions similar to a Caesarian. Clamps were used to stop circulation from uterus to fetus at term. Then the fetus was quickly removed and EEG tracings made. Various lengths of time were used. No resuscitation was needed in rabbits rendered anoxic up to five minutes. The nature of the respirations are described as are the tracing of electroencephalogram with ample illustrations. Convulsions did not occur in the animals deprived of oxygen for short periods of time. Convulsions with subsequent death occurred in animals given Cardiozol.

In autopsy studies the parts of the nervous system most recently elaborated phylogenetically were the first to be affected.

Other workers in this field are also cited and their conclusions given.

Allen, Santa Fe, N. Mex.

Microcephalic Children from Consanguineous Marriages. J. van den Bosch, Nederl. tijdschr. geneesk. 99:3773 (Dec. 10) 1955.

The author gives some typical examples of hereditary microcephaly as illustration of the eventual influence of consanguinity on the occurrence of abnormalities among the offspring. The hereditary form of microcephaly probably depends on a recessive gene of inconsiderable frequency. So one can expect a high percentage of consanguinity between the parents of homozygotic microcephalic children. This is confirmed by the date of this study. Five pedigrees are described of families which are living already during many centuries in isolated places. Isolated groups with a limited choice of marriage which have existed for centuries should be regarded as families. The frequency of the gene for microcephaly is much higher among the few people of such a group than in the total population of the country. Prevention is possible by discouragement of consanguineous marriage in general and between inhabitants of isolated parts, particularly if transmitters are found among the common ancestors in pedigree of isolated groups.

van Creveld, Amsterdam.

Aetiology of Congenital Malformations. J. Langman and F. van Faassen, Nederl. tijdschr. geneesk. 99:2119 (July 16) 1955.

The influence of a lowered metabolism of the mother animal on the development of the embryo is investigated by partial extirpation of the glandula thyroidea.

A number of experimental animals is operated upon before pregnancy and another group after fertilization. The group operated upon before pregnancy were found to have a lower number of embryos per pregnancy. There was a high percentage of resorption; ossification was retarded and sometimes abnormal; there were some cases of cleft palate and/or harelip, and hemorrhages from the jaws and hindlegs. In a high percentage all degrees of degenerative symptoms were found in the lenses. There were also regenerative changes of the lens and several cases of coloboma and anophthalmia. Often there was considerable plication of the retina. These anomalies may be due partly to oxygen deficiency. The influence of the thyroid

gland upon the proteinmetabolism and other metabolism processes are of important significance. There is no doubt that a complex of factors is due to the congenital malformations. The degree and form of hypothyroidism is of great influence upon the severity and frequency of the congenital malformations.

While the control group showed no defects of the eyes, it is suggested that this kind of malformation is not due to hereditary factors. The correlation between dysfunction of the thyroid and oxygen deficiency is discussed.

VAN CREVELD, Amsterdam.

CONGENITAL ANOMALIES AND HYPOMETABOLISM. J. Bos, Nederl. tijdschr. geneesk. 99:2141 (July 16) 1955.

A woman patient had six miscarriages and two children with congenital anomalies in succession. When it was discovered that her basal metabolism was considerably lowered, she was treated with Thyranon during her later pregnancies; after this she gave birth to five healthy children.

Some of her sisters had similar experiences; the sister whose basal metabolism was normal had healthy children.

It appears in the literature that in districts where goiter is frequently found the percentage of congenital anomalies is higher. The question remains whether the exogenous influence of the thyroid gland is solely responsible or the dysfunction is a factor superimposed on an endogenous disposition.

VAN CREVELD, Amsterdam.

OBSERVATIONS REGARDING CONGENITAL HARE-LIP AND CLEFT-PALATE. A. TAVARES, Lattante 26:617 (Oct.) 1955.

The incidence of cleft palate and harelip in the neighborhood of Oporto in northern Portugal is quite high, varying from 5 to 14 cases per 10,000 births in the various hospitals. It was not possible to link this incidence with the occurrence of rubella or other infections in the mothers during the first three months of pregnancy. An hereditary factor seemed to have played a role in only 4 of more than 200 cases. Consanguinity was present in no case. Nutritional and vitamin deficiencies in the mother are a much more likely cause. Operations for the correction of harelip are recommended at 2 to 3 months of age, and of cleft palate at 18 to 20 months.

HIGGINS, Boston.

ANGIECTASIS AND HYPOTROPHY: CONGENITAL VASCULAR CHANGES AND THEIR SEQUELLAE. C. ZUNIN and G. P. ZAPPA, Lattante 26:623 (Oct.) 1955.

A baby boy was born with perineal hypospadius and a marked venous angiectasis involving the posterior right thigh and the gluteal region. Six weeks later, definite hypotrophy of the entire right leg was apparent. It was doubtless due to vascular inefficiency. The case is classified as belonging to the Klippel-Trénaunay-Parkes-Weber syndrome.

HIGGINS, Boston.

Newborn

ELECTROLYTES IN THE NEWBORN INFANT. A. BALLABRIGA, Rev. Españ. Pediat. 11:309-314 (May-June) 1955.

The author studied the electrolytic composition of blood in 20 normal newborn infants beginning from birth to 12 hours and from 12 hours to 4 days and from 4 to 7 or 9 days, depending on whether adult values were achieved by 7 or 9 days.

His median figures are less than those obtained by Graham and others. He believes this has a direct relation to the nutrition of the mother during pregnancy but has not been able to work out the correlation.

The studies were made on sodium, potassium, chlorides, total proteins, inorganic phosphorus, alkaline reserve, etc.

Methods are described.

ALLEN, Santa Fe, N. Mex.

ADVANTAGES OF PYRIDOSTIGMINE BROMIDE (MESTINON) AND EDROPHONIUM CHLORIDE (TENSILON) IN THE TREATMENT OF TRANSITORY MYASTHENIA GRAVIS IN THE NEONATAL PERIOD. HALCUTT MORE, The New England J. Med. 253:1075 (Dec. 15) 1955.

A case of transitory myasthenia gravis in a newborn infant, demonstrating the urgency

of correct diagnosis and prompt treatment, is reported. The use of pyridostigmine bromide (Mestinon) proved to be of great help because it produced fewer of the undesirable muscarinic side effects that were alarming while neostigmine was being given. Edrophonium chloride (Tensilon) helped determine the proper dose of pyridostigmine.

In the past, women with myasthenia gravis have been warned not to become pregnant. The use of these drugs so greatly facilitates the management of such an infant that women with myasthenia gravis can expect a greater chance of survival for their offspring.

WHEELOCK, Washington, D. C.

DIABETIC EMBRYOPATHY. S. NORDIO and C. ROSSO, Minerva Pediat. 7:1379 (Nov. 3) 1955.

An 8 months diabetic para II gave birth to a 3200 gm. infant after a difficult forceps delivery. The mother had been receiving insulin during the pregnancy. The infant had tachycardia, marked edema, and mild icterus; blood counts showed that 94% of the nucleated cells were erythroblasts. Two hours after the birth, the child went into convulsions and died shortly afterward. At autopsy a cerebral hemorrhage was found; this is believed to have caused the death and convulsions. A diagnosis of diabetic embryopathy was made, after other likely causes of the blood findings were ruled out. Both the mother and the child were Rh negative; their bloods were compatible on agglutination tests. Reports from the literature reveal that children of diabetic mothers are very prone to have erythroblastosis.

HIGGINS, Boston.

TREATMENT OF WEAKLY SUCKLING OF INFANTS. F. M. G. OTTO, Med. Klin. 50:1748, 1955.

In the course of eight years Pervitin was given to 41 infants where sound feeding was undesirable for various reasons to stimulate suckling. In nine cases the results were good or very good. Of these three were uncomplicated premature infants without further complications, three had dyspepsia, one of these was a premature infant, one was dystrophic, one in a state of pretoxicosis, and one had a diabetic mother. When successful the difficulty was overcome within 24 hours with a dosage of 0.2 to 1 mg. per diem. given in one dose or in two doses. This low dosage was tolerated well. It is not recommended to use the drug in all instances of weak suckling. It is given for a few days. When the result was evident the medication was stopped entirely.

Acute Infectious Diseases

GAMMA GLOBULIN IN INFECTIOUS DISEASES. J. G. VAL BANERES, Arch. Pediat., Barcelona 5:667-687 (May-June) 1955.

The author gives some of his findings in the use of gamma globulin in the treatment of infectious diseases in children. To be effective it must be given early. It is very effective in certain infections when used with penicillin.

In the study on hemolytic Streptococcus infections, for example, the temperature curve and the sedimentation rate fell faster with both penicillin and gamma globulin than with penicillin alone. Complications were lessened also by the use of gamma globulin.

He includes many graphs.

ALLEN, Santa Fe, N. Mex.

PENICILLIN REACTIONS IN CHILDREN: A STUDY OF THE VALUE OF THE SKIN TEST IN PENICILLIN SENSITIZATION. ABE MATHESON and LAWRENCE ELEGANT, J. Allergy 26:415 (Sept.) 1955.

An aqueous solution of sodium penicillin G was used as a skin test on 397 children, age 1 to 14 years. If a negative scratch test was obtained then an intracutaneous test was done.

"Three hundred and ninety of a group of 391 children who had received penicillin injections on many occasions did not demonstrate skin sensitivity to same. Approximately 4 per cent of this group of children gave histories of vague symptoms only suggestive of serum sickness type of reaction following penicillin injections.

"When another group of six children who had experienced severe constitutional reactions following administration of penicillin was similarly tested, the following results were obtained. Four of the five children who had immediate or accelerated reactions and one child who had severe, delayed, constitutional symptoms had immediate positive skin tests to penicillin. In two of three such cases, when passive transfer skin tests were performed, the tests were positive and indicated the presence in the blood of reagins to penicillin.

"A negative skin test with penicillin does not rule out a potential anaphylactic-like reaction resulting from a subsequent injection of penicillin.

"Anaphylactic-like reactions from penicillin administration may occur in children who have previously had no reaction from administration of this antibiotic.

"It is our opinion that an immediate positive skin test with penicillin in children who have had penicillin contact indicates the presence of potential clinical sensitization. When such a child, in addition, presents a history of symptoms resulting from previous penicillin administration, further injection of penicillin will likely result in a constitutional reaction. In such cases, if penicillin is the sole effective antibiotic, its oral use should be tried."

HOYER, Cincinnati.

THE VIRAL ETIOLOGY (INFLUENZA) OF AN EPIDEMIC OF CATARRHAL CROUP. F. PANIZON and F. CANTARUTTI, Clin. Pediat. 37:620 (Aug.) 1955.

During January and February, 1955, an epidemic of catarrhal croup occurred in Padua; 39 young children, 27 of them under 2 years of age were admitted to the wards of the Pediatric Clinic. Thirty-three of the patients had fever and nineteen dysphonia. The onset was rapid in 14 of the cases. The duration was less than 5 days in 12 cases, and over 10 days in 10. Four developed tracheobronchitis; seven required tracheotomy, five in the early stages and two later. The bacterial flora from the larynx was usually of a mixed type; in 8 cases staphylococci prevailed and in 14 streptococci of various types. As the etiology was apparently of a viral nature, Hirst's tests were made in 12 of the cases for the serum titer toward the Influenza viruses A, A', and B. In each case, there was a marked and increasing titer to type B.

HIGGINS, Boston.

EPIDEMIC MYALGIA OF THE NECK. M. SCARZELLA, Minerva Pediat. 7:657 (June 2) 1955.

Five case reports are given of children who had the typical symptoms and findings of "epidemic myalgia of the neck" during the summer of 1954. The predominating symptoms were diarrhea, fever, headache, asthenia, and spasm and pain in the neck muscles. The duration of the acute symptoms was from five to seven days. By that time the pain in the muscles of the neck had begun to regress; it was wholly gone about two weeks after the onset. Three of the children had a leucopenia, and two had normal white counts. Spinal fluid findings were normal. Agglutination tests were made on the sera of four of the children; three showed positive to the Coxsackie virus B_3, and one was positive to the Coxsackie virus B_4.

HIGGINS, Boston.

PATHOGENESIS AND ETIOLOGY OF ACUTE INFECTIOUS LYMPHOCYTOSIS. H. J. BURGSTEDT, Monatsschr. Kinderh. 103:401-407 (Sept.) 1955.

The pathologic picture of acute infectious lymphocytosis is that of reticuloendothelial reaction with hyperplasia of small lymphocytes in the sinuses of lymph nodes and bone marrow. There is release of these cells into the peripheral blood stream.

This disease should be considered as a specific infection with an initial stage of communicability, an index of infectivity of about 50%, and an incubation period of two to three weeks.

Clinical observations and serologic characteristics are indicative of a viral etiology. Attempts to produce the disease in animals have been unsuccessful. There is a possibility of a syntropic relationship between the causative agent of the disease and lamblia enteritis as seemed to have been the case in the instance reported by the author in this paper.

HARTENSTEIN, Syracuse, N. Y.

CONTRIBUTION TO THE PROBLEM OF LISTERELLOSIS IN THE NEWBORN. K. BORN, Arch. Kinderh. 151: Band. 2. Heft. 1955.

Description is given of the case of a seriously ill icteric premature infant admitted at the age of 2 days with skin emboli, liver and spleen enlargement, erythroblastosis, and purulent meningitis in spite of absent neurological manifestations. The diagnosis was ascertained by bacteriological findings of Listeria in the blood and spinal fluid. Bacteriological findings in the mother were negative. Animal experiments and incidence in premature infants suggest prenatal transmission. Umbilical and vaginal infections have to be considered. The eastern districts of Germany obviously show a predominance. Septic signs, liver and suprarenal involvement are frequent; the meninges are less frequently affected. In milder cases the diagnosis can easily be missed, since asphyxia, circulatory manifestations, and convulsions will also occur in premature infants for other reasons.

GOTTSTEIN, Chicago.

Infections of the Tonsils Treated with Bismuth and Chloramphenicol. A. Montero Rodriguez, Acta. Pediat. Españ. 140:315-320 (May) 1955.

The author who previously made a study of the treatment of tonsillitis in children, using bismuth suppositories and sulfonamides and also a group in which he used penicillin, now reports on 20 cases of children with tonsillitis resistant to most forms of treatment.

The results were excellent. Only two suppositories were needed, and there were no relapses. Some of the cases treated were of the pseudomembranous angina type. No deleterious side-effects were noted.

Allen, Santa Fe, N. Mex.

Treatment of Pertussis with Largactil (Chloropromazine) and Chloromycetin. R. Rubino Castro, Acta. Pediat. Españ. 150:424 (June) 1955.

The author describes briefly his experience in the treatment of 50 children with Chloromycetin and Chloropromazine giving the dosages and the rationale for such treatment. He had no ill effects and quick recoveries, but he remarks that much more study of the type of epidemics and controls would be necessary to make any conclusions scientific from the standpoint of statistics.

Allen, Santa Fe, N. Mex.

Chronic Infectious Diseases

Tuberculosis in Infants, 1948-1954: Results of a Survey. A. Witte. Monatsschr. Kinderh. 103:433-437 (Oct.) 1955.

The author studied 1200 infants with tuberculosis. Mortality dropped from 46% in 1948 to 11.8% in 1953. This was due to a 26.9% decrease in the generalized form of the disease and to more effective and intensive tuberculostatic treatment.

Among generalized tuberculosis the following forms were included: miliary with and without meningitis, meningitis with military, osseous and ear involvement, tuberculid and phlyctenular conjunctivitis.

Primary tuberculosis was considered to be primary pulmonary with and without local complications (atelectasis, pulmonary infiltration, perforation of Bronchi, bronchogenic spread, pleurisy, progressive primary tuberculosis), tuberculosis due to ingestion.

In 1948, fifty-eight of the tuberculous infants did not receive tuberculostatic drugs. The principle of today's treatment consisted of the use of tuberculostatic drugs. Agents used were para-aminosalicylic acid, streptomycin, and isoniazid, the latter having become the most important weapon. Daily doses used were streptomycin, 30-40 mg/kg. I. M., PAS, 300 mg/kg. orally, and isoniazid, 10 mg/kg. orally.

Treatment of choice for miliary tuberculosis was a combination of streptomycin and isoniazid. In primary tuberculosis the single drug regimen was as effective as the combination. No patients receiving isoniazid developed tuberculous meningitis.

Hartenstein, Syracuse, N. Y.

Measles in the Course of Tuberculous Meningitis Under Streptomycin Therapy. I. Lanza, Minerva Pediat. 7:662 (June 2) 1955.

Eight children developed measles while undergoing treatment with streptomycin for tuberculous meningitis. Two of the children died; they were rather young (15 months), were in the early stage of the treatment (third week), and were in a precarious condition at the time of the onset of the measles. The deaths occurred some weeks after the measles attack; four children (2 to 4 years old) developed the measles between the 40th and 70th days of treatment. The measles ran its usual course; shortly afterwards the status of the meningitis showed remarkable improvement, especially in the spinal fluid findings. It is suggested that the antibodies against the measles contagium had also been of therapeutic benefit against the tubercle bacilli. Each of the children recovered. Two children (5 years old) contracted the measles in the late stages of the streptomycin therapy; the measles did not interfere with a normal and satisfactory recovery.

Higgins, Boston.

Bronchial Complications in Primary Tuberculous Infections of Children. L. Pietrantoni and A. Vago, Minerva Pediat. 7:933 (Aug. 25) 1955.

The bronchial complications of primary tuberculosis in children usually come under one of the following headings.

I. Stenosis of the bronchus from extrinsic pressure of a gland, with or without inflammation of the mucosa.
II. Such stenosis with perforation and a bronchial-glandular fistula.
III. Scar formation at the site of the perforation and fistula.
IV. Bronchiolitis.
V. Obstructive emphysema or atelectasis or pulmonary collapse.
VI. Aspiration bronchioalveolitis.
VII. Bronchiectasis and pulmonary fibrosis.

These complications should call for such examinations as bronchoscopy and bronchography. Eleven such cases are reported with illustrations of x-ray films and of the bronchoscopic findings in color.

HIGGINS, Boston.

BRONCHOGRAPHIC STUDIES IN CHILDREN WITH PULMONARY TUBERCULOSIS. B. CARLETTI and L. PARENZAN, Minerva Pediat. 7:955 (Aug. 25) 1955.

Children with primary tuberculosis may be found by standard x-ray films to have areas of pulmonary pathology, such as atelectasis or a more serious bronchial lesion. In such cases bronchography, and possibly stratigraphy and bronchoscopy, is necessary to establish a diagnosis as to the type of the lesion, and whether it may be due to epituberculosis (allergy), or to a more serious condition. Twenty-six cases are reported with illustrations of x-ray films. No untoward sequellae followed the bronchoscopy, even in the infants.

HIGGINS, Boston.

CLINICAL AND STATISTICAL DATA AS TO MILIARY AND MENINGEAL TUBERCULOSIS IN CHILDREN UNDER TWO YEARS OF AGE. B. E. DI GIACOMO, Minerva Pediat. 7:667 (June 2) 1955.

The cases of 20 infants under 2 years of age are reported. Cures were obtained in 2 out of 3 cases of miliary tuberculosis, in 3 out of 5 cases with both miliary and meningeal tuberculosis, and in 4 out of 12 cases of tuberculous meningitis. The source of the contagion was determined in 19 of the cases; in 14, one or both of the parents were the contacts; it was most frequently the nursing mother. Treatment was with streptomycin and in the more recent cases with PAS or isoniazide. The most important factors in obtaining a cure are early diagnosis and initiation of the treatment.

HIGGINS, Boston.

Diseases of Blood, Heart and Blood Vessels, and Spleen

TWO CASES OF SICKLE-CELL ANEMIA IN NATIVE ALGERIAN CHILDREN. R. CABANNES and R. VENEZIA, Pédiatrie 43:209, 1955.

The authors present two cases of sickle-cell anemia in two white children aged 2½ and 12 years, respectively, and describe detailed studies of one case, including sickling tests and electrophoretic studies of the hemoglobin.

GLASER, Baltimore.

TREATMENT OF LEUKEMIA. H. BEGEMANN, Deutsche med. Wchnschr. 80:850 (June 3) 1955.

The various methods of treatment of leukemia are reviewed. Triethylenmelamin is of use in cases of lymphatic leukemia under certain conditions. Myleran and colchicine are discussed. In acute leukemia of children folic acid antagonists are recommended in combination with ACTH or cortisone. Other drugs are considered as well as x-ray treatment and transfusions. In cases of chronic leukemia the prognosis has not become better, and in acute leukemia only transitory remissions have been obtained.

AMBERG, Rochester, Minn.

RADIOLOGIC ASPECTS OF OPERABLE HEART DISEASE: OBSERVATIONS ON THE PREOPERATIVE APPROACH TO CONGENITAL ANOMALIES. HERBERT L. ABRAMS, Radiology 65:31-49, 1955.

The author, believing that the roentgenographic examination adds greatly to the precision in the diagnosis of operable heart disease, discusses the acyanotic and cyanotic anomalies and furnishes clinical and other data gained by EKG, angiocardiography, cardiac catheterization, and by physical and radiological examinations. Illustrations are presented of pulmonary stenosis, patent ductus arteriosus (with and without reverse flow), ventricular septal defect,

coarctation of the aorta, endocardial fibroelastosis, tetralogy, pulmonic stenosis, tricuspid atresia, truncus arteriosus, and Ebstein's anomaly. Useful charts are included.

ANSPACH, Riverside, Ill.

NEOPLASIA IN CHILDREN TREATED WITH X-RAYS IN INFANCY FOR THYMIC ENLARGEMENT. C. L. SIMPSON, L. H. HEMPELMANN, and L. M. FULLER, Radiology 64:840-845, 1955.

A study of the subsequent history of the 1400 of 1722 children who received x-ray therapy to the thymus between 1925 and 1951 reveals a high incidence of neoplasia. This incidence is much higher in treated siblings than in untreated infants or in the general population. This especially held true in leukemia and in tumors of the thyroid gland. In the latter a high correlation existed between the form of treatment and the occurrence of the neoplasm and, according to the authors, must be suspected as a possible factor in etiology. A serious limitation of the interpretation of this data is the absence of a proper control group of untreated infants with enlarged thymus glands.

In the author's list of malignant neoplasia six cases of leukemia in a group of seven died within six months after x-ray treatment. It seems logical to this reviewer that the shadows seen on the chest roentgenograms were due to the leukemia and not to enlarged thymus.

ANSPACH, Riverside, Ill.

ENDOCARDIAL FIBROELASTOSIS: ROENTGEN APPEARANCE, W. R. EYLER, ROBERT F. ZIEGLER, JAMES J. SHEA, and GEORGE W. KNABE, Radiology 64:797-809, 1955.

In infants endocardial fibroelastosis usually reveals an enlarged globular heart and marked prominence of the vessels during failure. This does not hold true in older patients. Seven of the author's eight cases were under 3 years of age. All came to autopsy, and it was possible to examine the thickened endocardium caused by fibroelastosis. The location and degree of involvement varied in the different cases. There are no clinical, electrocardiographic, roentgenographic, or physiologic findings available at this time which make a differential diagnosis possible from the other members of "primary myocardial diseases," namely, anomalous origin of the left coronary artery from the pulmonary artery, glycogen storage disease, tumors of the heart, medial necrosis of the coronary arteries, and idiopathic myocarditis. Endocardial fibroelastosis may occur as an isolated cardiac abnormality. Aortic stenosis may be an associated finding, as well as coronary artery arteriosclerosis. The endocardial changes may be secondary to other abnormalities.

ANSPACH, Riverside, Ill.

X-RAY DIAGNOSIS OF ASYMPTOMATIC RHEUMATIC CARDITIS IN CHILDREN. I. RADNÓTI and F. HELL, Monatsschr. Kinderh. 103:274-276 (May) 1955.

X-ray and fluoroscopic examinations were performed on 178 ambulatory children with asymptomatic rheumatic carditis and on 200 normal children serving as controls.

Rheumatic activity was proved by history, physical findings, sedimentation rates, serial electrocardiograms, and clinical course of the illness. Two radiological findings were used for diagnostic purposes: (1) Isolated enlargement of the left atrium and (2) changes in heart size with the Valsalva maneuver, decrease in heart size being considered the reaction of the normal heart.

Positive radiological results were found in one-third of the children with asymptomatic rheumatic carditis. Therefore, it was concluded that positive x-ray and fluoroscopic findings were pathognomonic of, whereas negative results did not rule out, carditis.

HARTENSTEIN, Syracuse.

"DIFFERENTIAL SYSTOLIC BLOOD PRESSURE" IN AMBULATORY CHILDREN WITH CARDITIS WITH MINIMAL SYMPTOMS. I. RADNOTI-RECHT, Monatsschr. Kinderh. 103:297-300 (June) 1955.

Ambulatory children with carditis productive of minimal symptoms exhibited a fall in systolic blood pressure on deep inspiration which was found to be greater than the normal drop of 10 mm. The author called this phenomenon "differential systolic blood pressure." This finding was found to be valuable in establishing a diagnosis in the majority of patients and disappeared in a number of patients as recovery took place.

HARTENSTEIN, Syracuse, N. Y.

POLYCYTHEMIA ASSOCIATED WITH A RENAL TUMOR. Q. B. DEMARSH and W. J. WARMINGTON, Northwest Med. 54:976 (Sept.) 1955.

A case report and review of the literature of polycythemia associated with renal tumor.

The patient reported was followed for 10 years, 5 years before surgery and 5 years after surgery. A benign adenoma of the right kidney was removed. The polycythemia has not returned five years after surgery.

DOCTER, Seattle.

HORMONES IN THE TREATMENT OF ACUTE RHEUMATIC FEVER. EDITORIAL, New England J. Med. 253:478 (Sept. 15) 1955.

In the *New England Journal of Medicine* for January, 1954, Massell reviewed the divergent opinions of many workers concerning the value of ACTH and cortisone in the treatment of acute rheumatic heart disease. No comparison was made with the effects produced by the other antirheumatic drugs.

In March, 1954, a joint report from investigators in the United Kingdom, the United States, and Canada was published wherein the comparative results of the treatment of rheumatic fever with ACTH, cortisone, and Aspirin were elaborated.

Since this report, two further studies have been made, in Pittsburgh and Salt Lake City, and the conclusions drawn were favorable to the concept that the influence of steroid therapy on the clinical course of acute rheumatic fever is beneficial and the organic cardiac residuals are diminished.

Dorfman, one of the participants of the joint study, criticizes the latter conclusion because properly controlled experiments were not carried out. He concludes his commentary as follows:

"The weight of evidence would seem to indicate that treatment with cortisone, hydrocortisone or ACTH results in a more prompt response of certain manifestations of rheumatic fever, including some that are indicative of carditis. It would seem reasonable to treat patients with severe carditis with adequate doses of these substances. Hormone treatment of chronically active patients or those with severe damage has so far been unrewarding, and treatment of patients with little or no cardiac involvement would seem unnecessary in view of the excellent prognosis of such patients when treated with salicylates. Although the use of large doses of hormones for long periods of time may offer some promise, the potential dangers are sufficiently great as to cast doubt on the application of such a regimen except in highly restricted circumstances."

WHEELOCK, Washington, D. C.

CHROMATOGRAPHIC STUDY ON THE HEMOGLOBIN OF PATIENTS WITH CONGENITAL HEART DISEASE. P. C. GAMARELO and A. ACTIS-DATO, Minerva Pediat. 7:553 (April 28) 1955.

Chromatographic studies were made on the bloods of 58 patients with congenital heart disease; 46 of the patients were cyanotic; in several instances blood was taken before and after a patient had had a cardiac operation to relieve the cyanosis. In no instance did the behavior of the hemoglobin chromatographically differ from the hemoglobin of normal persons.

HIGGINS, Boston.

ELECTROCARDIOGRAPHIC AND ANGIOCARDIOGRAPHIC STUDY OF A CASE OF THE WOLFF-PARKINSON-WHITE SYNDROME, WITHOUT PAROXYMSAL TACHYCARDIA, IN A GIRL WITH ROGER'S DISEASE. R. BULGARELLI, Minerva Pediat. 7:535 (April 28) 1955.

An electrocardiogram revealed that a 5-year-old girl with a patent interventricular septum had also the Wolff-Parkinson-White syndrome. She had, however, never had any attacks of paroxysmal tachycardia. X-ray films and physical examination revealed an enlarged right ventricle. An angiocardiogram was done with the child suffering no untoward symptoms; no passage of the contrast media was observed from the right to the left ventricle; a small amount, however was observed to pass from the left to the right ventricle.

HIGGINS, Boston.

THE WHITE BLOOD COUNTS TAKEN DURING THE EARLY HOURS AND THE FIRST DAYS OF LIFE. S. NASSO and A. VERGA, Minerva Pediat. 7:735 (June 30) 1955.

White blood counts were made on a group of infants at birth and repeated 2, 4, 6, 8, 24, 48, 72, 96, 120, and 144 hours later. The total counts varied from 10,200 to 30,500 (mean 15,000) at birth; the counts tended to fall gradually until the mean count was 9500 forty-eight hours later. At birth the mean percentage of polymorphonuclear neutrophiles was 47; it rose to 74% after 6 hours but had again fallen to 51% after 96 hours. The mean percentage of lymphocytes at birth was 40, after 8 hours 17, and at 96 hours 36. Eosinophile counts were made on 50 babies on the same schedule, the method of Randholf being used. The eosinophile counts in the premature infants were highest, mean 450; they were next highest in babies born

spontaneously, mean 340. In infants born after a difficult labor the mean was 250, while in infants with markedly prolonged labor the mean count was 50. The degree of stress experienced by the infant during birth seems to be reflected directly in the leucocyte counts.

HIGGINS, Boston.

THE SYNDROME OF WOLFF-PARKINSON-WHITE IN A TWO YEAR OLD GIRL. G. RUSSO, Minerva Pediat. 7:285 (March 10) 1955.

A electrocardiogram, taken on a 2-year-old girl during an attack of paroxysmal tachycardia, revealed the typical findings of the Wolff-Parkinson-White syndrome.

HIGGINS, Boston.

A RELATIONSHIP BETWEEN THE SERUM PROTEIN CONSTITUENTS AND THE RED BLOOD CELL SEDIMENTATION RATE. P. MUGNAINI, Clin. Pediat. 37:333 (May) 1955.

The red blood cell sedimentation rate and the electrophoretic picture of the serum proteins were done on the blood of each of 15 patients, 5 with rheumatic disease, 5 with tuberculosis, and 5 with other infections. A definite relationship was observed between the RBC sedimentation rate and the $alpha_2$ globulin content; the faster the sedimentation rate the higher was the $alpha_2$ globulin content.

HIGGINS, Boston.

A CASE OF ACUTE EOSINOPHILIC LEUKEMIA. S. LI MOLI, Clin. Pediat. 37:217 (March) 1955.

A girl of 10 years after a 4 months illness was found to have a RBC of 900,000, Hb of 18%, and a WBC of 2400, with 12% P.M.N. and 88% lymphocytes; she was bleeding and apparently in a state of aplastic anemia. On bone marrow smears practically the only nucleated cells seen were erythroblasts and eosinophilic myeloblasts. Treatment with ACTH caused a reduction of the eosinophiles in the marrow but was ineffective therapeutically.

HIGGINS, Boston.

THE USE OF COBALT IN SOME COMMON ANAEMIAS OF CHILDHOOD. B. L. COLES, Arch. Dis. Childhood 30:121 (April) 1955.

Fifty cases of anemia in childhood were treated with cobalt, and satisfactory results were obtained in all but one case. All had types of anemia usually resistant to iron therapy.

Marrow studies before and after treatment showed an erythroid hyperplasia in 9 of 12 cases.

Reticulocytosis was not marked in the children studied. There were no toxic effects in the dosage used.

The possible mode of action of cobalt in the therapy of anemia is discussed.

KELLY, Milwaukee.

FULMINANT NORMOCHOLESTEREMIC XANTHOMATOSIS (HISTIOCYTOSIS X). MARTIN G. GOLDNER, and BRUNO W. VOLK, A. M. A. Arch. Int. Med. 95:689 (May) 1955.

The authors present an excellent review of the new unified concept of the diseases of the reticulum-cell system. According to this new concept, such syndromes as Hand-Schüller-Christian disease, Letterer-Siwe disease, and eosinophilic granuloma of the bone are now thought to represent merely the acute or chronic and the localized or disseminated form of the same basic pathologic process. The new entity has been called eosinophilic normocholesteremic xanthomatosis granuloma, or histiocytosis X. This new concept is based mainly on the fundamental interrelationships of the histological lesion. The authors also present a case report of an instance of this disease in an aged patient.

JONES, Chicago.

Diseases of Lungs, Pleura, and Mediastinum

IDIOPATHIC PULMONARY HEMOSIDEROSIS. DIETRICH BURCKHARDT AND CHRISTIAN VOGEL. Monatsschr. Kinderh. 103:455-460 (Oct.) 1955.

There have been 45 cases of idiopathic pulmonary hemosiderosis reported to which the authors add a case of their own. The disease has its onset in childhood and is characterized by pulmonary hemorrhages. Hemoglobin is metabolized only to a small degree, most of it being deposited in pulmonary tissue as hemosiderin.

The clinical picture consists of a severe anemia due to blood loss, low blood iron, and migratory chest x-ray findings. Crises with dyspnea, fever, and occasional abdominal pain occur. The majority of patients experience hemoptysis. Demonstration of so-called "heart failure cells" in sputum, gastric aspirate, or fluid obtained from pleural taps confirm the diagnosis.

Congenital or acquired diminution of elastic tissue in the lung is considered to be the cause of this condition. In addition, allergic factors seem to play a role. This may explain cures after splenectomy which seems to have been the only successful treatment for idiopathic pulmonary hemosiderosis. Otherwise, the disease is fatal in two to five years.

One spontanous cure, four cures after splenectomy, and 3 cases with improvement (without splenectomy) have been reported.

HARTENSTEIN, Syracuse, N. Y.

BULLOUS LUNG DISEASE IN INFANTS. M. NEGRI, Minerva Pediat. 7:1386 (Nov. 13) 1955.

Bullae were found on x-ray films of the chests of six infants. Before making a definite diagnosis, the possibility that one is encountering a lung abscess or a localized pneumothorax must be considered. The history of a Staphylococcus infection or the finding of staphylococci on throat cultures suggest that these organisms are an important etiological cause of the bullae. The bullae may disappear in short order, or they may persist for a long time. Treatment should be medical (usually by antibiotics); surgery is necessary only when tension in the bullae is causing asphyxial symptoms.

HIGGINS, Boston.

SPIROMETRIC DETERMINATIONS OF THE VITAL CAPACITY AND OF THE MAXIMUM VOLUNTARY BREATHING CAPACITY OF HEALTHY CHILDREN. E. SEGAGNI and P. C. GAMALERO, Minerva Pediat. 7:1444 (Nov. 10) 1955.

Data were collected as to the vital capacity and the maximum breathing capacity of 50 boys and 50 girls 5 to 12 years of age. Maximum breathing capacity is the maximum volume of air which can be breathed voluntarily in one minute. The findings are plotted on curves according to the height of the child. The volumes obtained with the boys were always higher than those of the girls of the same height. After the 130 cm. height is reached on the curves (about 9 years old), the rate of increase in both vital capacity and maximum breathing capacity is much more rapid.

HIGGINS, Boston.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

USE OF CARBONATED BEVERAGES IN PEDIATRIC EXCRETORY UROGRAPHY. JOHN W. HOPE and FRANCISCO CAMPOY, Radiology 64:66-71, 1955.

A review of 200 urograms obtained with the use of a carbonated beverage (Pepsi Cola) to distend the stomach in infants and young children revealed good visualization of the pelvo calyceal collecting system in 190. The preparation consisted of dehydration for one feeding in infants and nothing by mouth for 10 to 12 hours in older children. Infants were given 2 oz. of the cold carbonated beverage and older children 6 to 12 oz. following the preliminary film and administration of intravenous contrast medium. Additional carbonated beverage was given after the five-minute film if there was insufficient gaseous distention of the stomach to push away the overlying shadows of the kidneys. This usually occured in 25 minutes from the time of the injection.

ANSPACH, Riverside, Ill.

SEVERE JAUNDICE—TREATMENT WITH CORTISONE—CURE. M. JEUNE, A. CHARRAT, and Y. LÖAEC, Pédiatrie 43:198, 1955.

A 6½-year-old female was hospitalized in comatous condition seven days after onset of fever and one day after appearance of jaundice. Red blood count: 5,890,000, white blood count: 22,000. Low serum albumin, high globulin, and positive liver tests.

The patient received, aside from intravenous dextrose with electrolytes, stimulants, penicillin, 25 mg. ACTH upon admission, and cortisone I.M. 150 mg. for three days and then in diminishing doses for nine days. Only on the third day the child began to come out of coma, but the jaundice increased and the liver enlarged and temperature remained elevated for several months, returning to normal only when cortisone was resumed for

several days. Liver biopsy showed diffuse fatty infiltration, negligible traces of sclerosis and slight signs of inflammation.

Five months after the onset of the disease the child was reexamined and found cured.

GLASER, Baltimore.

Nervous Diseases

ELECTROENCEPHALOGRAPHIC FINDINGS IN INFANTS DURING SLEEP INDUCED BY 3-METHYL-1-PENTYN-3-OL (DORMISON). E. LANZONI, Clin. Pediat. 37:323 (May) 1955.

When 3-methyl-1-pentyn-3-ol was given on doses of 250 mg. to infants under 6 months of age and in doses of 500 mg. to infants older than 6 months, a restful sleep was induced in from 5 to 30 minutes. The encephalographic tracings on these sleeping infants were those found during normal sleep of average depth. This drug is therefore recommended for clinical encephalographic studies in preference to a barbiturate, which usually leads to high voltage and rapid brain waves.

HIGGINS, Boston.

ADENOSINTRIPHOSPHORIC ACID AND ENCEPHALOGRAMS. S. NORDIO AND F. PISTONE, Clin. Pediat. 37:199 (March) 1955.

Adenosintriphosphoric acid (ATF), in addition to its metabolic functions, should also affect the nervous system by reason of its phosphorus content and its acetylizing action. To test this surmise, nine children, six with liver dysfunction and three with allergic disturbances, were given 10 to 15 mg. ATP parenterally each day for 6 to 10 days. Encephalograms following hyperventilation were recorded for each child before and after the course of medication. Originally the tracings showed a general slowing of the rhythm as well as paroxysms of very slow waves. After medication, a more normal response to the hyperventilation was observed in six of the cases; the responses in the allergic patients were equivocal.

HIGGINS, Boston.

NEURO-SURGICAL ASPECTS OF EPILEPSY IN CHILDREN. M. MILLETTI, Clin. Pediat. 37:3 (Jan.) 1955.

In a 57-page article, the surgical treatment of epilepsy is discussed, and 14 case reports from the Maggiore Ospedale in Bologna are given. A course of medical therapy in epilepsy should not be decided upon without first being sure that there is not some causative cerebral lesion which may be corrected surgically, as tumor, abscess, atrophic area, or vascular abnormality; prolonged delay may result in further cerebral damage and less chance for a surgical cure; therefore an immediate thorough examination, including encephalography, of each epileptic child is imperative.

Epilepsy was present in 19% of cases of brain tumor in children 2 to 18 years of age; it was not present in any case where the tumor was subtentorial; it was a frequent finding (54%) when the tumors were in the cerebral hemispheres.

Surgical treatment for epilepsy was also successful in many cases where there were atrophic cerebral lesions, as microgyria, porencephaly, and post-traumatic meningeocerebral scars.

If vascular lesions are treated surgically, a subsequent cerebral hemorrhage may be averted.

HIGGINS, Boston.

THE TREATMENT OF EPILEPSY IN CHILDREN WITH MYSOLINE. L. BRIZIO, Clin. Pediat. 37:137 (Feb.) 1955.

Mysoline is a drug of chemical structure similar to phenobarbitol, an oxygen atom being replaced by two hydrogen atoms in the barbituric acid molecule.

Twenty-eight epileptic patients under 12 years of age were under Mysoline treatment (0.5 to 1.25 gm. daily) over a period of from 6 to 15 months. In about two-thirds of these patients, other commonly used anticonvulsive drugs had been found ineffective. Of 13 patients with grand mal, 5 were completely relieved of attacks, while 5 others showed definite improvement. Excellent results were obtained in two cases of Jacksonian

epilepsy, and in four of petit mal. Of eight cases of focal epilepsy, complete control of the attacks occurred in two, and improvement in four.

HIGGINS, Boston.

Diseases of Genitourinary Tract

THERAPY OF THE NEPHROTIC SYNDROME IN CHILDHOOD. HEINRICH WIESENER, Monatsschr. Kinderh. 103:379-385 (Aug.) 1955.

Thirty children with nephrosis were followed for a 29-year period. There were eight deaths attributable to the disease, none of them since 1945. Ten patients were considered cured; their follow-up periods were from 3 to 19 years.

Eight children were treated with either ACTH or Conteben or both. Of these patients five were considered cured with follow-up periods of one to three years. One patient in the treated group was improved.

HARTENSTEIN, Syracuse, N. Y.

FERTILITY OF MEN WITH CRYPTORCHISM. J. RABOCH and Z. ZAHOR, Schweiz. Med. Wchnschr 85:1196-1199 (Dec. 3) 1955.

Fertility or possible fertility is determined by enumeration of functionally effective spermatozoa and, in some instances, by testicular biopsies, in adults. With unilateral cryptorchism the descended testis may have intact spermiogenesis, but in other cases this was found injured or absent even when the testis appears normal on palpation. Persons with bilateral cryptorchism operated upon after the 14th year of life or not operated upon were, as a rule, azoospermic. In persons operated upon before that time, the results were somewhat better. It is concluded that in cases without hope for a spontaneous descensus during puberty, surgery should be performed before the 10th year of life. Even when the testes are incapable of functioning, surgical interference is recommended for psychological reasons.

AMBERG, Rochester, Minn.

DIFFUSE GLOMERULONEPHRITIS IN CHILDREN, J. A. ALEMANY SITJA, Arch. Pediat., Barcelona 5:527-569 (March-April) 1955.

The author prefers to classify the glomerulonephritides as acute diffuse proliferation glomerulonephritis and chronic diffuse membranous glomerulonephritis. He prefers this last term to nephrotic syndrome or lipoid nephrosis.

He explains his reasons for his preference. He then reviews the literature from 1900 to the recent work of C. F. Piel and group in San Francisco.

There is detailed description of the two types of nephritis, clinically. Laboratory differences, and pathological descriptions are described including the electrophoresis curves of plasma proteins.

He gives much attention to the discoveries which have been made in the experimental nephritis in animals.

ALLEN, Santa Fe, N. Mex.

Diseases of Ductless Glands; Endocrinology

CHANGES IN THE GONADOTROPHS OF THE RAT PITUITARY AFTER GONADECTOMY. H. D. PURVES and W. E. GRIESBACH, Endocrinology 56:374-386 (April) 1955.

In a preceding paper evidence was presented for the presence in the anterior pituitary of the rat of two specific types of gonadotrophic basophiles. Of these, the peripherally situated, coarsely granulated type appeared to be concerned with the production of FSH, while the central, finely granulated type was assumed to produce LH. In this paper observations on gonadectomised rats are reported, in which the resulting cell changes in the anterior pituitary are correlated to changes in the gonadotrophic potency of tissue from the same gland. It is shown that the changes which occur in the follicle-stimulating and luteinizing potencies of the glands within certain times after gonadectomy are paralleled by characteristic changes in the two types of gonadotrophic basophiles. The evidence obtained by these observations supports the results of the preceding paper.

JACOBSEN, Buffalo.

RAT PLACENTAL HORMONAL ACTIVITIES CORRESPONDING TO THOSE OF PITUITARY MAMMOTROPIN. ESTEN W. RAY, STUART C. AVERILL, W. R. LYONS, and RUTH E. JOHNSON, Endocrinology 56:359-372 (April) 1955.

Many earlier reports have emphasized the importance of the placenta as an endocrine organ. In studies on the hormonal factors concerned with the maintenance of pregnancy few findings have been so striking as those showing that the rat placenta is capable of carrying out roles usually assigned to the pituitary.

Further comparisons of the placental and pituitary factors reported here indicate that the rat placenta at an early stage of development contains a substance (or substances) with luteotropic, mammotropic, lactogenic, and crop-sac-stimulating activities. Compared with pituitary mammotropin (prolactin), it is potent in the first three of these activities and weak in the last.

JACOBSEN, Buffalo.

PHOSPHORUS METABOLISM OF THE ADRENAL GLAND: EFFECT OF HYPOPHYSECTOMY AND ADMINISTRATION OF ACTH ON THE INCORPORATION OF RADIOACTIVE PHOSPHATE INTO THE RNA NUCLEOTIDES. J. E. LOGAN, F. C. HEAGY, and R. J. ROSSITER, Endocrinology 56:455-460 (April) 1955.

The current interest in the role of ribonucleic acid (RNA) in cellular function made it desirable to compare the phosphorus metabolism of the RNA in a tissue during low functional activity with that of the same tissue during high functional activity—for instance, the adrenal gland of the hypophysectomized rat compared with the adrenal gland of rats treated with ACTH.

In the experiments described in this paper, the incorporation of P^{32} into the RNA of the adrenal gland was studied.

It is concluded that in the adrenal gland of hypophysectomized rats there is (*a*) a decrease in the rate at which inorganic P^{32} passes from the extracellular to the cellular portion of the gland and (*b*) a decrease in the rate of formation of organic phosphorus compounds (e. g., lipid phosphorus, RNA nucleotides) from the cellular inorganic phosphate. It is suggested that these changes, and those in the opposite direction that follow the administration of ACTH, may reflect changes in the over-all energy metabolism of the adrenal gland rather than specific effects on the constituent under study.

JACOBSEN, Buffalo.

THE EFFECT OF HYPOPHYSECTOMY, CRYPTORCHIDISM, ESTROGEN AND ANDROGEN UPON THE LEVEL OF HYALURONIDASE IN THE RAT TESTIS. EMIL STEINBERGER and WARREN O. NELSON, Endocrinology 56:429-444 (April) 1955.

The presence of a "spreading factor" is well known in testes of rats, rabbits, and guinea pigs which is identical with an enzyme isolated from autolysates of Type II pneumococci and which is designated as hyaluronidase in view of its capacity to depolymerize hyaluronic acid.

The purpose of this investigation has been to examine the changes in hyaluronidase concentration in testes of cryptorchidized, hypophysectomized, estrogen-treated, and testosterone-treated rats, employing throughout the study a standard method of extraction and determination of the enzyme.

On the basis of the evidence at hand the spermatid seems to be the testicular cell that has the most significant role in the production of hyaluronidase.

JACOBSEN, Buffalo.

THE RELATION OF ASCORBIC ACID TO ADRENOCORTICAL FUNCTION DURING COLD STRESS. WALTER M. BOOKER, FRANCES M. DACOSTA, JAMES R. TUREMAN, CLEO FROIX, and WILLIAM JONES, Endocrinology 56:413-419 (April) 1955.

Experiments are described showing the effects of ascorbic acid, cortisone, and combinations of these substances on survival of intact and adrenalectomized mice. The suggestion is made that ascorbic acid may facilitate the "handling" of potassium in the adrenalectomized animals subjected to cold stress.

JACOBSEN, Buffalo.

ROLE OF IODINE DEFICIENCY IN THE PRODUCTION OF GOITER BY THE REMINGTON DIET. A. A. AXELRAD, C. P. LEBLOND, and H. ISLER, Endocrinology 56:387-403 (April) 1955.

None of the foodstuffs used in the Remington diet, not even sodium chloride, was essential for the induction of goiter by a diet sufficiently low in iodine. The prevention of such goiters by a small dose of iodine completes the demonstration that iodine deficiency is the essential factor in their production.

JACOBSEN, Buffalo.

THE EFFECTS OF LOCALLY APPLIED ESTROGEN ON THE PUBIC SYMPHYSIS AND KNEE JOINT IN CASTRATED MICE. E. S. CRELIN and A. L. HAINES, Endocrinology 56:461-470 (April) 1955.

After puberty a sexual dimorphism of the pelvis develops in mice. At this time the medial ends of the pubic bones at the symphysis in the female undergo partial resorption. During the first pregnancy the ventromedial part of the pubes is resorbed further and an interpubic ligament replaces the symphysial cartilage. Similar changes occur in intact females and gonadectomized mice when estrogens are injected. But the normal and induced pubic-bone resorption follow a similar pattern. While this is occurring no other articular cartilage of the body undergoes such a marked change. Why the interpubic tissue and pubes respond so specifically to estrogen and why the hormone produces such a consistent-pattern of pubic-bone resorption is unknown. In the present experiment estrogen was applied locally to the bones and soft tissues at the pubic symphysis and knee joint.

The pattern of pubic-bone resorption in the present experiment was the same as that described after subcutaneous estrogen injections.

The results show that the gonads and their secretions need not be present for a sexual dimorphism of the bony pelvis to develop in mice.

JACOBSEN, Buffalo.

REDUCTION OF PITUITARY CONTENT OF ACTH BY CORTISONE. GORDON L. FARRELL and GERT LAQUER, Endocrinology 56:471-473 (April) 1955.

Dogs were treated with cortisone, 100 mg. per day, for 14, 44, and 71 days. The ACTH content was found to be depressed to 54% of control levels in 14 days, 3% in 44 days, and 2% in 71 days.

The observed profound decrease in pituitary ACTH content following cortisone treatment adds further evidence that the adrenocortical atrophy reported in long-term cortisone therapy is mediated by suppression of pituitary activity.

JACOBSEN, Buffalo.

Surgery and Orthopedics

RESECTION OF THE INFERIOR VENA CAVA IN THE REMOVAL OF A GANGLIONUEROMA. D. L. B. FARLEY, Great Ormond St. J. No. 3, p. 2, Winter 1954-1955.

By means of vena caval resection a benign tumor which otherwise could not be operated upon was removed from the abdomen of a 5-year-old girl.

The examination of the child, special investigation, and the successful operation are reviewed. No complications resulted.

McGUIGAN, Evanston, Ill.

Teeth and Dentistry

THE EVENTUAL STATUS OF CHILDREN WHO HAD BEEN TREATED SURGICALLY FOR HYPERTROPHIC STENOSIS OF THE PYLORUS. B. CARLETTI and W. FUMAGALLI, Minerva Pediat. 7:627 (June 2) 1955.

Over a period of nine and one-half years, 15 young infants were operated upon for hypertrophic stenosis of the pylorus by the Fredi-Ramstedt method. The immediate clinical results were excellent. Four months to six and one-half years later, it was possible to reexamine 10 of these children; none of them reported any abnormal gastrointestinal symptoms; after barium meals, several films showed muscular hypertonicity in the prepyloric region and a few rough folds in the gastric mucosa.

HIGGINS, Boston.

A CASE OF CONGENITAL NEUROBLASTOMA WITH AN EXCEPTIONALLY FAVORABLE OUTCOME. L. BUFFONI, Minerva Pediat. 7:1285 (Oct. 20) 1955.

An infant was born after a difficult labor with a tumor under the skin in the fifth interspace in the axillary line. When the child was seen three months later, he had enlarged axillary glands, very large liver and spleen, and other small tumors on the skin. A biopsy of the tumor was done, and the diagnosis by two pathologists was neuroblastoma. The child was doing very badly but began to improve three months later. When he was again seen at the age of 16 months, the tumors had disappeared, the liver and spleen were no longer enlarged, and the child appeared normal for its age.

HIGGINS, Boston.

PROPHYLAXIS WITH FLUORINE TABLETS AND THEIR DOSAGE. H. R. HELD, Schweiz. med. Wchnschr. 85:11 (Jan. 1) 1955.

Investigations in pregnant women and in children 8 to 12 years of age proved conclusively that orally given sodium fluoride is resorbed and increases the fluoride content of teeth. Of sodium fluoride in tablet form, about 80% is resorbed, and of calcium fluoride, about 60% is resorbed. The dosage has to be chosen so as to supply the deficit of the drinking water with the aim to bring it up to 1 mg. per 1000 cc. No untoward effects were noted. It is not necessary to consider the fluorine content of solid food when calculating the deficit in water. Tables are given denoting the numbers of tablets containing 0.25 mg. F, to be given of NaF or CaF_2 at various ages and weight of children, when the drinking water contains 0.1 mg. F per 1000 cc.

AMBERG, Rochester Minn.

Miscellaneous

THE CAUSES OF ACUTE POISONING IN CHILDREN SEEN AT THE TOXICOLOGY CLINIC OF THE UNIVERSITY OF FLORENCE. P. PERITI, Minerva Pediat. 7:232 (Feb. 24) 1955.

Five hundred fifty-two cases of acute poisoning in children over a period of 11 years are recorded. Two hundred thirty-four of the cases were from medicines or chemicals, being mostly in children 1 to 6 years old; one hundred forty-nine cases were from food toxins, being mostly in children 3 to 7 years old. There were 46 cases from poisonous mushrooms, 27 from disinfectants, 23 from strong alkalis, 9 from strong acids, and 24 from petroleum products.

The authors draw the following conclusions:

"(1) Poisonings are much more frequent between the end of the first year of life and the beginning of the fourth.

"(2) The chemical and pharmaceutical products, which are of common use in home life, are in most of the cases responsible for the poisoning; the other substances are very seldom involved.

"(3) The principal source of the poisonings is represented by those drugs, which look like sugar or candies.

"(4) In about 90% of the poisoning cases caused by drugs or various chemical substances, the fault is of the child, who has taken advantage of the parents' absence: in the other cases the poisonings are due to a mistake made by an adult."

HIGGINS, Boston.

THE TREATMENT OF INTOXICATIONS IN CHILDHOOD. L. LENDLE, Deutsche Med. Wchnschr. 80:1220-1124 (Sept. 2) 1955.

The paper gives a review of poisoning by various agents in childhood with special emphasis on treatment.

AMBERG, Rochester Minn.

TOTAL TRANSPOSITION OF THE VISCERA ASSOCIATED WITH OTHER CONGENITAL MALFORMATIONS. JESUS MARTINEZ FERNANDEZ, Acta Pediatrica Espanola No. 150 pp. 425-431 (June) 1955.

The author describes a 7-year-old girl who was brought in for an unimportant cough but upon examination there was a total transposition of all viscera as well as syndactylism of all fingers and toes. There was no familial history of syndactylism. The child's mental development was normal for her age. Photographs and x-rays are included. This combination is supposed to occur once in 1500 radiographic studies.

ALLEN, Santa Fe, N. Mex.

News and Comment

GENERAL NEWS

Specialists certified in Pediatric Allergy.—The following pediatricians were certified in Pediatric Allergy following an examination held in Chicago on June 13, 1956.

Leo B. Burgin, Brookline, Mass.
Claude A. Frazier, Asheville, N. C.
John P. McGovern, Houston, Texas
Allen D. Shapiro, Newburgh, N. Y.

The two following pediatricians whose names were not included on a previous list were certified in Pediatric Allergy at an examination in Atlantic City, N. J., on June 9, 1955.

Vincent J. Fontana, New York.
Lewis J. Schloss, New York.

ANNOUNCEMENTS

Continuation Course in Pediatrics.—The University of Minnesota announces a continuation course in Pediatrics for Pediatricians to be held at the Center for Continuation Study from Sept. 25 to 27, 1956. This year's course will feature panel discussions of pediatric emergencies, endocrine disorders, heart diseases, allergic conditions, and behavior disorders as well as lectures on other pediatric topics of current interest. Dr. Francis Howell Wright, Professor and Head, Department of Pediatrics, University of Chicago Medical School, will be guest speaker for the course, which will be presented under the direction of Dr. John A. Anderson, Professor and Head, Department of Pediatrics.

All registrants are invited to attend the Irvine McQuarrie Lecture on Wednesday evening, Sept. 26, and the annual scientific meeting of the Northwestern Pediatric Society at Bayport, Minn., on Friday, Sept. 28.

Lodging and meal accommodations are available at the Center for Continuation Study.

Congress on Rheumatic Diseases.—The Ninth International Congress on Rheumatic Diseases will be held at Toronto, Ontario, Canada, from June 23 to 28, 1957. This quadrennial function of La Ligue Internationale contre le Rhumatisme will be held under the auspices of the Canadian Rheumatism Association.

The Program Committee invites contributions to the scientific program of the Congress and is anxious to receive reports on current clinical or basic research dealing with any aspect of the rheumatic diseases.

Those offering papers for consideration should submit a 200- to 300-word abstract not later than Jan. 1, 1957. Abstracts should be submitted in triplicate in the language in which the paper is to be read. If an abstract is submitted in a language other than English, it will be helpful, though not essential, if it can be accompanied by an English translation.

All correspondence should be directed to The Ninth International Congress on Rheumatic Diseases, Post Office Box 237, Terminal "A," Toronto, Ontario, Canada.

SOCIETY NEWS

American Pediatric Society Officers.—The following officers and new members were elected at the 1956 meeting of the American Pediatric Society.

President, Dr. Daniel C. Darrow; Vice-President, Dr. Samuel Levine; Secretary-Member, Dr. F. Howell Wright.

Treasurer, Dr. Aims C. McGuiness; Recorder-Editor, Dr. Stewart H. Clifford; Council

New Members: Forrest H. Adams, Los Angeles; James Bosma, Salt Lake City, Utah; Ronald L. Denton, Montreal, Canada; Paul A. di Sant'Agnese, New York; James N. Etteldorf, Memphis, Tenn.; Lytt I. Gardner, Syracuse, N. Y.; T. Campbell Goodwin, Cooperstown, N. Y.; Weston M. Kelsey, Winston-Salem, N. C.; Robert Klein, Pittsburgh; Harry Medovy, Winnipeg, Canada; Ralph E. Moloshok, New York; Theodore C. Panos, Galveston, Texas; Helmut P. Seckel, Chicago; Frederic N. Silverman, Cincinnati.

Society for Pediatric Research Officers.—At the 1956 meeting of the Society for Pediatric Research the following slate of officers was elected for 1957:

President, Dr. William Wallace; Vice-President, Dr. Harry Waisman; Secretary-Treasurer, Dr. Sydney S. Gellis; Member of Council for three years, Dr. John Osborn; Member of Council for one year, following his leave of absence, Dr. Henry Kempe.

The following new members were elected to the Society:

Dr. Guilio Barbero, Dr. Thomas Boggs, Dr. Robert M. Chanock, Dr. Marvin Cornblath, Dr. Joaquin Cravioto, Dr. J. Frederick Eagle, Dr. Heinz J. Eichenwald, Dr. Silvester Frenk, Dr. Ruth Gross, Dr. Melvin Grumbach, Dr. Albert Hennessy, Dr. Gerald Kerrigan, Dr. Sidney Kibrick, Dr. Lula O. Lubchenco, Dr. Robert McAllister, Dr. Claude J. Migeon, Dr. C. Arden Miller, Dr. Richard Rowe, Dr. Julius Rutzky, Dr. Richard T. Smith, Dr. Robert A. Ulstrom.

PERSONAL

Dr. Parrott Named Physician-in-Chief of Children's Hospital.—Dr. Robert H. Parrott, on the staff of the National Institutes of Health (NIH) Clinical Center at Bethesda, Md., has been named Physician-in-Chief at Children's Hospital and assumed his new duties July 1. As Physician-in-Chief, Dr. Parrott will supervise the medical care provided for patients at the Hospital and will head up the Hospital's education and research programs.

Appointment of Dr. Sydney S. Gellis.—Dr. Sydney S. Gellis has been appointed Professor of Pediatrics at the Boston University School of Medicine and Director of Pediatrcis at the Boston City Hospital. This appointment starts Sept. 1, 1956. He will continue his appointment as Physician, Children's Medical Center, and will also be Lecturer in Pediatrics at the Harvard Medical School.

Appointment of Dr. Robert A. Aldrich.—Appointment of Dr. Robert A. Aldrich, associate professor of pediatrics at the University of Oregon, as head of the University of Washington School of Medicine's Department of Pediatrics, was approved Saturday by the Board of Regents.

Dr. Aldrich, 38, will assume his new position August 1. He will succeed Dr. Walter B. Seelye, head of the Pediatrics Department since it was established in 1947. Dr. Seelye will resign September 1 to retire to his farm near Issaquah.

A member of the University of Oregon Medical School faculty since 1951, Dr. Aldrich has done important research on rheumatic fever and the relatively new field of porphyrin metabolism.

He is a 1939 graduate of Amherst College, and he received his doctor of medicine degree in 1944 from Northwestern University. After two and one-half years in the U. S. Navy during World War II, Dr. Aldrich spent three years as a resident at the University of Minnesota hospitals and served from 1949 to 1951 as an associate and consultant in the Section on Pediatrics of the Mayo Clinic.

He is immediate past president of the Western Society for Pediatric Research and is a member of the council of the Society for Pediatric Research. He is also chairman of the regional section on medical education of the American Academy of Pediatrics, and he is on the editorial board of the A. M. A. JOURNAL OF DISEASES OF CHILDREN.

Books

BOOKS RECEIVED

We acknowledge receipt of the following books. Only those books will be reviewed which the Editorial Board finds suitable for this journal.

Histamine—CIBA Foundation Symposium. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. Price, $9. Pp. 472, with one illustration. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

Neurology and Psychiatry in Childhood Proceedings of the Association. Edited by Rustin McIntosh and Clarence C. Hare. Price, not given. Pp. 504, with several illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1954.

Allergy in Childhood. By Jerome Glaser. Price, $12.50. Pp. 529, with 42 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

Case Studies in Childhood Emotional Disabilities. Vol. 2. Edited by George E. Gardner. Price, $5. Pp. 368. American Orthopsychiatric Association, 1790 Broadway, New York 19, 1956.

Annual Review of Medicine. Vol. 7. Edited by David A Rytand. Price, $7. Pp. 611. Annual Reviews, Inc., Stanford, Calif., 1956.

The Mentally Retarded Patients. By Harold Michal-Smith. Price, $4. Pp. 203. J. B. Lippincott Company, East Washington Square, Philadelphia 5, 1956.

Pediatric Nursing. Ed. 3. By Gladys S. Benz. Price, $5.25. Pp. 634, with 114 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1956.

Treatment of the Child in Emotional Conflict. By Hyman S. Lippman. Price, $6. Pp. 298. McGraw-Hill Book Company, Inc., 330 West 42nd Street, New York 36, 1956.

Die Pathologie des kindlichen Pankreas. By Gerhard Seifert. Price, DM 52. Pp. 151, with 109 illustrations. Georg Thieme, Hainstrasse 17-19 Aufg. C Leipzig, Germany, 1956.

Patterns of Mothering. By Sylvia Brody. Price, $7.50. Pp. 446. International Universities Press, Inc., 227 West 13th Street, New York 11, 1956.

Auxologia e Auxopatia. By Guido Calderoli. Price, not given. Pp. 67. Guido Calderoli, Via XX Settembre 79, Bergamo, 1956.

Behavior Problems of Children. By J. C. Marfatia. Price, Rs. 6/4. Pp. 159. The Association of Pediatricians of India, Back Bay View, New Queen's Road, Bombay 4, India. N. D.

Laboratory Tests in Common Use. By Solomon Garb. Price, $2. Pp. 160. Springer Publishing Co., 44 East 23rd Street, New York 10, 1956.

Urologie de l'enfance. By Gaston Lauret. Price, 3,900 francs. Pp. 446, with 330 illustrations. Expansion Scientifique Francaise, 15, Rue Saint-Benoit, Paris, 1956.

The Yearbook of Modern Nursing. Edited by Cordelia Cowan. Price, not given. Pp. 446, with 5 illustrations. G. P. Putnam's Sons, 210 Madison Ave., New York 16, 1956.

A Guide for the Study of Exceptional Children. By Willard Abraham. Price, $3.50. Pp. 276. Porter Sargent, 11 Beacon Street, Boston 8, 1956.

La Salud del hijo. By Juan P. Garrahan. Price, not given. Pp. 603. Libreria "El Ateneo" Editorial, Florida 340, Buenos Aires, Argentina, 1955.

Mental Health Planning for Social Action. By George S. Stevenson. Price, $6.50. Pp. 358. McGraw-Hill Book Company, Inc., 330 West 42nd Street, New York 36, 1956.

The Practice of Psychosomatic Medicine—As Illustrated in Allergy. By Hyman Miller and Dorothy W. Baruch. Price, $5. Pp. 196. McGraw-Hill Book Company, Inc., 330 West 42nd Street, New York 36, 1956.

Cerebral Palsy—Advances in Understanding and Care. By Viola Cardwell. Price $5. Pp. 625, with 81 illustrations. Association for the Aid of Crippled Children, Room 713, 1790 Broadway, New York 19, 1956.

Angiocardiographic Interpretation in Congenital Heart Disease. By Herbert L. Abrams and Henry S. Kaplan. Price, $11.75. Pp. 233, with 161 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

The authors of this book have successfully written in concise, easy to understand style a summary of accepted knowledge on the angiocardiographic diagnosis of congenital heart disease. In Section I there is a discussion of the general considerations in contrast radiographic studies of the heart and great vessels. Angiographic technique, equipment, the opaque media used, and reactions to angiocardiography are described without burdensome detail, and statements borrowed from the literature are well documented by adequate bibliography. They give a critical analysis of the complications to the procedure and definite recommendations to prevent or treat the complications. A schedule of recommended dosage for infants and children is given for the three most widely used contrast substances. Their chapter on the "General Principles of Angiocardiographic Interpretation" is a very good direct summary of the salient principles used to interpret contrast studies of the heart and great vessels. The authors have found that almost all of the abnormal findings visualized in the angiocardiographic examination of congenital heart disease can be condensed into one or a combination of more than one of nine basic alterations of filling of the heart and great vessels by the contrast media. In Section II the authors discuss the contrast diagnosis of the various congenital anomalies of the heart and great vessels singly devoting a chapter to each entity. The list of anomalies is very complete. Each anomaly is described briefly with a brief discussion of the pertinent clinical findings and other aids to diagnosis. The appendix to this book summarizes the findings in congenital heart disease in a table of differential diagnosis. Throughout the book the authors have presented their material in a concise but complete manner. It is well written, and the diagrammatic illustrations that accompany every radiographic reproduction makes the information clearly and quickly understood. It is the type of book that can be read from cover to cover and yet is organized well as a quick reference book on the subject. The authors are complimented on giving us a book that will prove very worth while to anyone interested in the radiographic diagnosis of congenital heart disease.

La rieducazione motoria delle paralisi cerebrali infantili. By A. Colli Grisoni. Price, not given. Pp. 194, with 38 illustrations. L. Cappelli, Via Farini 6, Bologna, 1955.

This book is the first to appear in the Italian language dealing with the reeducation of the cerebral spastic child. In the bibliography most of the articles dealing with physiology are by French authors, while those dealing with the reeducation are by Americans. The Neurological Institute of Milan maintains a Center or School for Motor Reeducation; the activities in this Center afford the background for the apparatus, methods, and therapeutic results described; the charts used in this clinic are reproduced, together with a table tracing the normal motor, mental, linguistic, and social development of the child. The first chapters of the book deal with the physiological and clinical aspects of the various types of cerebral paralysis. Then there follows a discussion of the methods applicable to the reeducation of each type—spasticity, dystonia, athethosis, and ataxia. A full chapter is devoted to the treatment of the speech difficulties met with in these cases. The enthusiasm of the author in her subject is contagious; if one is in Italy, a visit to this Clinic should be interesting and worthwhile.

The Office Assistant in Medical or Dental Practice. By Portia M. Frederick and Carol Towner. Price, $4.75. Pp. 351, with 55 illustrations. W. B. Saunders Company 218 West Washington Square, Philadelphia 5, 1956.

This is an excellent book designed to give instruction to the office assistant—secretarial hints for the nurse, or nursing hints for the secretary. Despite the fact that much must be taught individually to one's office assistant, a book of this nature can save a busy physician hours of time. The many practical hints given should make this book welcome to experienced office assistants as well as to neophytes.

Communicable Disease. Ed. 3. By Franklin H. Top. Price $18.50. Pp. 1208, with 109 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1955.

The third edition of this excellent text book lives up to the reputation of its predecessor. New chapters have been added on Cat Scratch Fever and on Histoplasmosis and many of the older chapters have been rewritten by collaborating authors to bring them up-to-date. In all, 24 collaborators have contributed to this volume among whom of particular interest to Pediatricians are, Drs. Amos Christie (Histoplasmosis), David D. Rutstein (Rheumatic Fever), Jonas E. Salk (Influenza), G. D. Cummings and W. W. Ferguson (Epidemic Diarrhea of the Newborn), and Warren E. Wheeler (Ophthalmia Neonatorum). From the first plate, an extremely fine color photograph of early measles, throughout the book there is an excellent collection of illustrations and figures. This book can be highly recommended to students and practicing physicians.

The Pediatric Years. By Louis Spekter. Price, $12.50. Pp. 734, with 20 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1955.

This book, consisting of some 700 pages and divided into six sections, is written by an author with extensive experience in a public health program for handicapped children and in the field of maternal and child health. It is intended as a single source of information for all workers caring for children.

Section I dealing with Trends in the Savings of Lives of Mothers and Infants and with care of the mother is in very brief and general terms and does not seem to have been given the importance it deserves in a volume of this magnitude. In Section II growth and development and daily care of children is discussed in such a way as to be of distinct value for nonmedical personnel. The chapter on the newborn and the premature infant, though too brief, is one of the better chapters of the entire book. Section III is the most voluminous and deals with many of the illnesses and categories of illnesses which children experience. Parts of it are in almost dictionary form while other portions are in considerable detail. Too little attention is given to prevention and too much to disease description. The chapters on Psychologic Considerations of the Child in the Hospital and Mental Deficiency give a brief but commendable picture of these subjects. Section IV considers the role and function of various professional workers, community responsibility in health and disease, and voluntary and official health agencies. School Health services are dealt with all too briefly. Section V on standards of service is well done and is one of the best. Section VI on pediatric procedures would seem to be out of place in a volume of this sort.

In attempting to produce a reference manual which would be of value to all professional workers dealing with children, the author has assumed a tremendous responsibility. One wonders if the objective can be achieved.

Community Programs for Mental Health. By Ruth Kotinsky and Helen L. Witmer. Price, $5. Pp. 362. Harvard University Press, Cambridge, Mass., 1955.

This book should be of general interest to all pediatricians and of specific interest to those physicians who, as part of their community responsibilities, are interested in supporting preventive mental health programs for children and parents.

This book provides an excellent over-all view of mental health promotion. Perhaps the most interesting is the discussion of the problems in evaluation. Saul W. Ginsburg, M. D., presents a clear and provocative picture of the mental health movement and its theoretical assumptions. Certainly today with so much emphasis on preventive and educational movements toward the goal of a "positive mental health approach," the attempt of certain agencies and bodies to apply an epidemiological approach to mental disease requires real thought and consideration for those of us active or interested in the emotional problems of our citizens.

In addition to theoretical considerations, there are sections of this book dealing with the setting up and management of community programs in mental health and sections on a description of mental health work in the schools, and those interested in research will find food for thought in the works of Dr. Jahoda and Dr. Howe.

Certainly, with the present emphasis on mental health, "the nation's number one health problem," this book might well find a place in the libraries of community-minded physicians.

Clinical Laboratory Diagnosis. Ed. 5. By Samuel A. Levinson and Robert P. MacFate.

Price, $12.50. Pp. 1246, with 257 illustrations. Lea & Febiger, 600 Washington Sq., Philadelphia 6, 1956.

The many recent advances in laboratory medicine make this a timely and worthwhile addition to any medical library. The material is presented in a clear, concise manner, with frequent use of the outline form and tables, which makes the desired information easy to find. However, clarity and subject matter are not sacrificed to gain brevity.

The pediatrician will find of special interest the chapters on The Kidneys, Hematology, Immunology and Serology, Cerebrospinal Fluid, General Bacteriology, Skin Tests, Laboratory Methods in Pediatric Procedures, Legal Medicine and Toxicology, as well as many others.

The author's objective to present to the medical student, intern, the resident physician, and the practicing physician, as well as the medical technologist, a suitable review of clinical laboratory diagnosis sufficient to meet their general needs is well met in this fifth edition.